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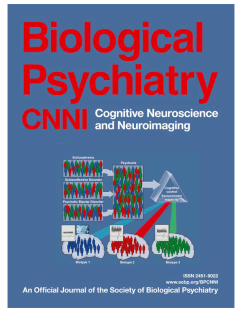

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Abstract:

Background: Cognitive ability is an important predictor of lifelong physical and mental well-being and impairments are associated with many psychiatric disorders. Higher cognitive ability is also associated with greater educational attainment and increased household income. Understanding neural mechanisms underlying cognitive ability is of crucial importance for determining the nature of these associations. In the current study, we examined the spontaneous activity of the brain at rest to investigate its relationships with not only cognitive ability, but also educational attainment and household income.

Methods: We used a large sample of resting-state neuroimaging data from UK Biobank (N=3,950).

Results: Firstly, analysis at the whole-brain level showed that connections involving the default mode network (DMN), frontoparietal network (FPN) and cingulo-opercular network (CON) were significantly positively associated with levels of cognitive performance assessed by a verbal-numerical reasoning test (standardized β ranged from 0.054 to 0.097, $p_{corrected}<0.038$). Connections associated with higher levels of cognitive performance were also significantly positively associated with educational attainment (r=0.48, N=4,160) and household income (r=0.38, N=3,793). Further, analysis on the coupling of functional networks showed that better cognitive performance was associated with more positive DMN-CON connections, decreased cross-hemisphere connections between the homotopic network in CON and FPN, and stronger CON-FPN connections (absolute β ranged from 0.034 to 0.063, $p_{corrected}<0.045$).

Conclusion: The present study finds that variation in brain resting state functional connectivity associated with individual differences in cognitive ability, largely involving DMN and lateral prefrontal networks. Additionally, we provide evidence of shared neural associations of cognitive ability, educational attainment, and household income.

Introduction

General cognitive ability is positively associated with higher educational attainment (1), better workplace performance (2), and with reduced risk of several mental and physical diseases (2–5). Identifying the associated neural mechanisms will help better understand the causes of these associations.

Studies have been conducted to explore the relationship between resting-state network and cognitive ability (6–8). Resting-state networks (RSN) involving lateral prefrontal cortex, such as executive control network and frontal-parietal network, have been previously reported to have positive associations attention and executive control (9). Newer evidence suggested that, other than prefrontal networks, the default mode network (DMN) is an important neurobiological marker for higher network efficiency as it is a metabolic and neural network hub for the whole brain (10; 11), and it is associated with a large number of positive sociodemographic variables (11). However, prefrontal networks and DMN show distinctive metabolic activity (12), and in certain tasks, they can be neuroanatomically antagonistic (13). The ambiguity of biomarkers for cognitive performance therefore limits the potential of using neural-network modeling for practical purposes like assisting clinical diagnoses and identifying the regional targets for neuronal interventions.

The variability of results in previous studies (11; 14; 15) may be due to relatively small sample sizes, often limited to 100 participants or fewer. This limitation is difficult to overcome using meta-analysis, as methods of extracting functional networks may vary considerably between studies. Therefore, there is a need for large-scale studies using a single scanner and consistent methods of estimating the association of RSN activity with consistently-collected social and psychological phenotypes to determine the relationship between resting functional connectivity and cognitive ability.

In the current study, we examined resting-state data from the first release of the UK Biobank imaging project (16; 17). Participants from 40 to 75 years old were recruited widely across the United Kingdom (16; 18; 19). For the resting-state fMRI (rs-fMRI) data used in the current study, 3,950 subjects underwent the cognitive assessment using a test of verbal-numerical reasoning (VNR; referred to in UK Biobank as a test of "fluid intelligence"). This measurement is genetically and phenotypically representative to the latent component of general cognitive performance (20; 21). This test had a test-retest reliability of 0.65 between the initial assessment visit in 2006-2010 and the first repeat assessment visit in 2012-2013 (21; 22). It also shows a significant genetic correlation with childhood general cognitive ability (r=0.81) (20).

In addition to the utility of analyzing a large sample, the present study benefited from examining the neural associations between educational attainment and household income. The rs-fMRI data were available for educational attainment and household income on samples of 4,160 and 3,793 subjects, respectively. Both education and household income show phenotypic correlations and shared genetic architecture with cognitive ability (21; 23); however, the associations between cognitive ability and these two variables with respect to functional connectivity remain unclear.

In order to address the above issues, our analyses were conducted following the order: (1) We examined whole-brain resting-state connectivity using a very large sample, to identify functional networks associated with cognitive performance (2) We then tested which resting-state connections were associated with educational attainment and household income, as these two traits are highly relevant to cognitive performance. (3) to determine which regions are involved with the above three traits, pairwise correlation analyses were conducted between neural associations of cognitive performance, educational attainment and household income on all connections over the whole brain. For these three steps, we conducted the analysis on a correlation matrix derived from high-resolution brain parcellation. Finally, (4) we moved on to examine the coupling between bulk resting-state networks based on a low-resolution parcellation, focussing on networks identified by the previous two whole-brain analyses.

Methods

Participants

The study was approved by the National Health Service (NHS) Research Ethics Service (reference: 11/NW/0382), and by the UK Biobank Access Committee (Project #4844). Written consent was obtained from all participants.

In total, 4,162 participants undertook a rs-fMRI assessment and passed the quality check undertaken by UK Biobank (http://www.fmrib.ox.ac.uk/ukbiobank/nnpaper/IDPinfo.txt) (Mean Age=62.20+/-7.56 years, Male=47.48%, 3576 (85.92%) White, 142 (3.41%) Asian, 31 (0.74%) Black and 142 (3.41%) mixed).

Imaging data

We used the network matrices from the IDPs (imaging-derived phenotypes) which were processed by the UK Biobank imaging project team(16). The detailed methods of the UK Biobank imaging processing can be found in a previous protocol paper(16). For clarification, these processes are described briefly below.

All imaging data were obtained on a Siemens Skyra 3.0 T scanner (Siemens Medical Solutions, Germany, see http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367).

Data pre-processing, group-ICA parcellation and connectivity estimation were carried out using FSL packages (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977) by UK Biobank. Briefly, pre-processing included motion correction, grand-mean intensity normalization, high-pass temporal filtering, EPI unwarping, gradient distortion correction unwarping and removal of structured artifacts(16).

Group-ICA were then performed on the preprocessed sample of 4,162 people, and two different ICAs were performed with the dimensionality (*D*) set as 100 and 25. The *D* determines the number of distinct ICA components. The dimensionality of *D*=100 infers a parcellation of high-resolution, whilst setting *D*=25 results in low-resolution parcellation, and larger functional networks that can be extracted as a single component(11; 16). After the group-ICA, noise components were discarded; this resulted in 55 components in 100-*D* ICA and 21 components in 25-*D* ICA that remained for further analysis. The maps of both ICAs can be seen at: http://www.fmrib.ox.ac.uk/datasets/ukbiobank/index.html.

Finally, connections between pairs of ICA components for each subject were estimated. We used the partial correlation matrices calculated using the FSLNets toolbox: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets. A partial correlation matrix was generated by controlling for the strength of other connections. The normalized estimation of partial correlation was conducted with an L2 regularization applied (rho=0.5 for Ridge Regression option in FSLnets). More details can be found in Miller et al.(2016) (16) and the URL: https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf.

The final 55*55 and 21*21 partial correlation matrices were used as measurements of functional connections. The two matrices are different. A 100*100 matrix has a much higher spatial resolution, therefore gives better spatial details in terms of identifying what regions involve in significant connections. On the other hand, a 25*25 matrix has a low spatial resolution, but it allows us to estimate the temporal synchronization between bulk networks that are well-known, such as DMN. Hence, the functional networks that were found in the whole-brain analysis were selected from the 21*21 matrix as NOI, connections between the NOI were tested.

Cognitive performance

A test of verbal-numerical reasoning (VNR) was carried out by UK Biobank according to the standard protocol (21; 24; 25). Questions of the test can be found in the Touch-screen fluid intelligence test protocol document: http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=100231). The data used in the present study were collected at the time of imaging assessment (N=3,950, Age=62.07+/-7.54, Male=47.47%). Descriptive statistics is presented in supplementary results and Figure S1.

Educational attainment and household income

Educational attainment and household income phenotypes were self-reported. The details are reported in the study website (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=100471, http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=100256). Descriptive statistics of educational attainment and household income are presented in supplementary results and Figure S1.

For educational attainment, we used a proxy which was validated in previous studies(20; 21). We created a binary variable was created to indicate whether or not university/college level education was achieved. This proxy covered 4,160 participants (Age=62.20+/-7.56, Male=47.48%).

Household income was determined by the average total income before tax received by the participant's household in five levels (see supplementary methods). This measure had 3,793 non-empty responses (Age=61.98+/-7.57, Male=49.04%).

Statistical methods

We used the partial correlation matrix as a measurement of functional connectivity. Values in the matrix are normalized correlation coefficients. A higher absolute value means stronger strength of connection, and the sign indicates whether the connection is positive/negative. To enable clearer interpretation of the results, the values of the connections were transformed into connection strength. This was achieved by multiplying the raw connection values with the signs of their mean value. This approach was used in a previous study by Smith *et al.*(2015) (11).

Analyses were performed in the following sequence: (1) A whole-brain analysis of the association between cognitive performance (VNR) and resting-state functional connectivity using the connectivity matrix derived from high-resolution parcellation. (2) Two separate whole-brain analyses on educational attainment and household income, respectively. (3) We then performed correlation analyses on the global functional connections predicted by the three phenotypic variables over all the connections in the 55*55 matrix over the whole brain, that is, testing whether the standardized effect sizes for the VNR score's link to functional connections were correlated with the corresponding effect sizes for educational attainment and household income. Two correlation analyses were then performed respectively on (a) the effect sizes of cognitive performance and educational attainment and (b) the effect sizes of cognitive performance and household income. (4) Network of interest.

This method has been validated in various previous studies as well as in the protocol paper for UK Biobank imaging project (16; 26).

The associations between brain connections and cognitive performance, educational attainment, and household income were tested by separate models using the linear GLM function in R (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/glm.html). Each trait was set as the independent variable in their individual models, and the connectivity matrix (high/low-resolution matrices, 55*55 for whole-brain analysis and the selected networks in 21*21 matrix for network-of-interest analysis) was set as the dependent variable. All of the models were adjusted for age, age^2, and sex.

False Discovery Rate (FDR) (27) correction was applied over each set of test over the whole brain as a unit (N_{test}=1,485 for 55*55 matrix, N_{test}=16 for connections of bulk networks) using the p.adjust function in R setting $q<0.05$ for significance level (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/p.adjust.html). All β-values reported in the results are standardized effect sizes.

Results

Whole-brain test of the association of cognitive performance with functional connectivity

A group-ICA was applied to parcellate the whole brain into 55 components, and the pair-wise functional connectivity between the components was estimated using FSLnets (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). The 55*55 partial correlation matrix was used for whole-brain analysis. To enable clearer interpretation of the results, the values of the connections were transformed into connection strength(11).

[Figure 1 insert here]

Better performance in VNR was significantly associated with 26 connections (absolute β ranged from 0.054 to 0.097, all $p_{corrected}<0.05$, $p_{uncorrected}<6.73\times10^{-4}$, see Supplementary Table S1). These include 18 connections that showed higher strength with higher VNR, and 8 connections that had lower strength of connection in people with higher VNR (Supplementary Table S1). The 18 connections largely involved the DMN, which includes bilateral posterior cingulate cortex (PCC), bilateral medial prefrontal cortex (PFC) and right temporal-parietal junction (TPJ), see Figure 1. Additional areas of right inferior PFC, dorsal anterior cingulate cortex (ACC) bilateral anterior insula and visual cortex were also involved. The connections that were weaker with better cognitive performance included bilateral lateral postcentral gyrus and superior ACC (Figure 1).

We then conducted permutation test on an updated sample of unrelated people (N=7,749). Half-sized samples (N=3,572) were selected and tested the distributions of the p values for the significant connections found in our initial findings. After 1,000 times of randomly selecting half of our sample, conducting analyses on them, and then compared the distributions of p values for the significant connections with the p values for the rest of connections (see supplementary materials). Two connections' p values were higher ($t>6.95$, $p<6.62\times10^{-12}$), and all others' were lower, which takes up 92.3% of the connections that were significant in the initial findings (all t ranged from -1076.88 to -2.21, all $p<0.028$, see in Figure S7).

Whole-brain tests on the association of educational attainment and household income with functional connectivity

There were 33 connections that showed significant associations with educational attainment (absolute β ranged from 0.103 to 0.161, all $p_{corrected}<0.05$, $p_{uncorrected}<8.53\times10^{-4}$ see Supplementary Table S2). Of these, the strength of 21 connections was stronger with higher educational attainment, whereas 12 were weaker. The regions involved in connections that were stronger with better educational attainment included regions in DMN and dlPFC. A large area of ACC was also involved. Connections that were weaker with higher educational attainment were located in the Inferior part of PCC and lingual gyrus (Figure 2).

[Figure 2 insert here]

For household income, 15 connections were significant, 11 of which were stronger with higher household income and 4 showed weaker connections (absolute β ranged from 0.060 to 0.082, all $p_{corrected}<0.05$, $p_{uncorrected}<4.27\times10^{-4}$ Supplementary Table S3). The regions of the connections that were stronger for higher household income again fell in similar regions as in tests of educational attainment and cognitive performance, which included PCC, medial PFC, ventral lateral PFC and dorsal lateral PFC (Figure 2). The areas that showed weaker connections for higher household income were smaller, which mainly included superior temporal lobe. Full lists of regions for the above results are presented in Table S4.

The spatial maps for the results of cognitive performance in VNR, educational attainment, and household income overlapped substantially (Figures 2 and 3). By performing correlation analysis at the standardized effect sizes of the whole brain (see Methods, Statistical methods), we found a correlation of r=0.47 (df=1,483, $p<2X10^{-16}$) between the global effect sizes for cognitive performance and educational attainment. The correlation between the effect sizes of cognitive performance and household income was $r=0.38$ (df=1,483, $p<2X10^{-16}$) (Figure 3).

Similar to the permutation test performed on VNR, the distributions of p values for 93.3% of the significant connections found in for educational attainment were lower than the mean p value for the rest of connections (all t ranged from -1429.77 to 11.54, all $p<4.22\times10^{-4}$, Figure S8) and all for household income were lower (all t ranged from -704.07 to -5.49, all $p<4.97\times10^{-8}$, see Figure S9).

[Figure 3 insert here]

Network-of-interest (NOI) test on VNR, educational attainment, and household income

The whole-brain tests showed that the connections associated with cognitive performance in VNR, educational attainment and household income were predominantly located within the DMN (covering medial PFC, PCC and TPJ), cingulo-opecular network (CON, covering ventral lateral PFC, and dorsal ACC) and frontoparietal network (FPN, covering dorsal lateral PFC and posterior parietal cortex). Therefore, DMN, CON, and FPN were selected as NOI from another group-ICA of lower resolution so these networks could be fully extracted (see Methods). The pairwise between-network coupling of these five networks (DMN was unilateral, and CON and FPN were separately extracted on each hemisphere) were tested to determine their association with cognitive performance, educational attainment, and/or household income. The above components can be viewed in Figure S2. The valence and values for the coupling of the above NOI were shown in Table 1. Similar with the analyses at whole-brain connectivity, the values of the connections were transformed into coupling strength before they were fed into the model.

There were 8 coupling between functional networks significantly associated with VNR performance out of 10 connections tested (all $p_{corrected}<0.05$, $p_{uncorrected}<0.035$. β reported below.). For educational attainment, 3 connections were significant, and none was found significantly associated with household income.

For the coupling between DMN and networks involving with lateral PFC, better VNR performance was associated with stronger positive connections between DMN and bilateral CON (stronger positive connection between DMN and left CON: $\beta=0.061$, $p_{corrected}=6.7X10^{-3}$; weaker negative connection of DMN with right CON: $\beta=-0.045$, $p_{corrected}=0.011$).

On the other hand, greater strength of coupling within the networks involving with lateral PFC was significantly associated with better cognitive performance. Stronger positive CON-FPN connection was also associated with higher VNR score. In the same hemisphere, people with better cognitive performance showed stronger positive CON-FPN connections (left CON-left FPN: β=0.044, $p_{corrected}$=0.011; right CON-right FPN: β=0.051, $p_{corrected}$=0.005), whilst across hemispheres, stronger negative CON-FPN connections were higher (left CON-right FPN: β=0.034, $p_{corrected}$=0.044; right CON-left FPN: β=0.043, $p_{corrected}$=0.011). Finally, higher VNR scores were associated with weaker cross-hemisphere connections between the homotopic network components (left-right FPN: β=-0.040, $p_{corrected}$=0.018. left-right CON: β=-0.063, $p_{corrected}=6.7X10^{-4}$). The above results are presented in Table 1 and Figure S3.

Educational attainment and household income had generally smaller associations with network coupling, and fewer significant connections were found. People with higher educational attainment showed a stronger positive connection between DMN and right FPN (β=0.104, $p_{corrected}$=0.004) and lower positive connection between DMN and right CON (β=-0.149, $p_{corrected}=1.99X10^{-5}$). A stronger positive connection between right FPN and CON was associated with better educational attainment (β=0.086, $p_{corrected}=6.24X10^{-3}$). No significant association between household income and the coupling of networks was found (all $p_{corrected}$>0.124).

For the connections that were significant for both cognitive performance and educational attainment, we performed mediation analysis using Lavaan in R to test whether the effect between educational attainment and bulk network connections were mediated by cognitive performance. Figure S6. Network connectivity was set as the predictor, and cognitive performance as the dependent variable. Educational attainment was specified as the mediator. We found that the association between rFPN-rCON and rCON-DMN connectivity and educational attainment was mediated by cognitive performance (18.4% and 76.2% of direct path mediated by indirect path respectively for each model, CFI = TLI = 1, see Figure S6).

Discussion

In the present study, we utilized a large population-based sample of ~4,000 participants and found that strength of connections involved with DMN regions, anterior insula, dorsal lateral prefrontal cortex in FPN and inferior frontal gyrus in CON were positively associated with performance in a verbal-numerical reasoning test. The brain regions associated with cognitive performance also overlapped with those related to educational attainment and household income. These above results were validated in a bigger updated sample of N>7,000 people. For cognitive performance in particular, better cognitive functioning was marked by a more strongly positive DMN-CON connection, weaker cross-hemisphere connections of the left-right CON and left-right FPN, and stronger CON-FPN connections.

We used a large sample and provided evidence that, in addition to the broadly suggested idea of lateral PFC, which involves dorsal lateral prefrontal cortex in FPN and inferior frontal gyrus in CON, playing a crucial role in cognitive processing, DMN was also associated with cognitive performance (β of connections positively associated with cognitive ability ranged from 0.054 to 0.097) (24; 28; 29). Previous studies showed that DMN serves as a hub for the whole brain (13). In comparison with other functional networks, DMN showed a higher metabolic rate in resting-state (12), stronger connections with the rest of the whole brain in both task-free and task-engaging situations (30), and a key role in maintaining basic levels of wakefulness/alertness in the brain (31). Higher efficiency within the DMN was reported to be associated with various cognitive functions, including memory (32), theory of mind (33), working memory (34), and performance in general intelligence tests (35). The high-level cognitive abilities mentioned above often involve the activity of multiple, spatially distant brain regions (32; 36). Therefore the DMN, as a communicative hub, contributes to functional efficiency over the whole brain (35), potentially producing better integration and cooperation in core regions that are important for cognitive tasks.

Additionally, the present study tested the coupling between networks of interest. Stronger positive DMN-CON coupling was associated with better cognitive ability (absolute β>0.045). In addition to the well-recognised task-positive lateral prefrontal cortex (therefore anti-correlated with the DMN), our findings in this large single-scanner sample lend substantial credence to increasing evidence that the CON itself (37; 38), and its positive coupling with the DMN in both resting-state (39) and event-related studies (40)) is highly pertinent for important aspects of cognitive performance. The role of the CON was related to maintaining task-engaging status (37; 41) and flexibly switching between the DMN and central executive network based on experimental context (42; 43). The experimental context in which CON and DMN were found to be simultaneously activated was often about goal-directed cognition (43), which involves self-driven retrieval of memory or learned experience and self-regulatory planning (15). As the DMN is associated with self-referential processing (13) and self-driven cognition like retrieval of personal experience (44) and planning (15; 45), positive coupling of the CON and DMN may indicate recruitment of self-referential and goal-oriented activity. Therefore successful DMN-CON coupling may be useful in maintaining internal mechanisms that support cognitive processing and long-term learning (43).

The connections between networks involving lateral PFC showed that better cognitive performance was associated with stronger CON-FPN connections (absolute β>0.034). This result is consistent with previous structural and functional findings that support the key role of prefrontal areas on cognitive performance (29; 46). We also found that better cognitive performance was related to between-hemisphere dissociation within networks (absolute $\beta>0.040$). Whereas this is the first time to our knowledge that this has been examined in a study of a large sample, such reduced structural connection between the left and right lateral PFC has been observed in schizophrenic patients with impaired cognitive performance(47). More lateralization of the brain is associated with better cognitive performance (48; 49), whereas, less lateralization, especially in prefrontal cortex, is related with reduced specialization of brain functions across hemispheres, therefore the advantageous anti-correlated connection we report here potentially denotes increased brain efficiency (48; 50).

The whole-brain connection map for cognitive performance overlaps substantially with those from educational attainment and household income. Further analyses showed that there were global correlations of cognitive ability with educational attainment ($r=0.47$) and with household income ($r=0.38$). GWAS studies found that cognitive performance and educational attainment share a similar genetic architecture ($r=0.906$) (1; 20). There was, in particular, an overlapping finding for educational attainment and cognitive performance in rFPN-rCON connection, and rCON-DMN connection. We found that cognitive performance significant mediated the association between NOI connectivity and educational attainment (Figure S6). The right-hemisphere connection for the two prefrontal networks (FPN and CON) may therefore reveal the association between education and executive control abilities, which was shows consistently associated with right lateral prefrontal cortex (51). Early life intelligence (relatively stable across the life-course (52; 53)) and educational attainment show partially overlapping associations with some structural brain measures in older age (54). Taken together, one interpretation of these data is that the functional hallmarks of a more 'intelligent' and better-educated brain are related to income by virtue of these temporally preceding factors. It could equally be the case that income confers additional lifestyle benefits that also influence these cerebral characteristics; the causal direction that gives rise to the highly overlapping functional connectivity reported here would be more adequately addressed with longitudinal multi-modal data.

A limitation for the current study is that the verbal-numerical reasoning test, as a brief measure, may not confer the same level of reflection on general cognitive ability as other longer, in depth general cognitive measures. The test-retest reliability was moderate, mainly because rather than the usual short time period between test and retest, this was performed in UK Biobank between 2-5 years which may contribute to the relatively low value. However, as previous studies found that verbal-numerical reasoning shared significant genetic and phenotypic correlation with the latent component of general cognitive performance (20; 21), it therefore confers adequate representativeness of general cognitive ability. Another limitation is that the sample covers an older age range, and there is potential bias to healthy, better-educated people. A notable strength of the present study is that we used a large sample, providing compelling evidence that both dorsal prefrontal areas and DMN were associated with cognitive ability, educational attainment and household income. To disentangle how multiple networks involved in the cognitive ability, we examined functional connectivity by estimating connections between brain components derived in two different resolutions, giving us another strength of studying both the connections over the whole brain and the connections of bulk intrinsic functional networks within a single dataset. Finally, in addition to visual checking of overlapping regions of the significant connections, we statistically compared the functional connectivity associated with cognitive ability, educational attainment and household income over the whole brain, giving a magnitude of neural associations among them.

Conclusion

The present study used a large, population-based sample, who provided multi-dimensional rs-fMRI data, and found substantial evidence for functional neural associations cognitive ability (verbal-numerical reasoning) both in whole-brain dynamics and the coupling for intrinsic functional networks. The findings also characterized the degree of rs-fMRI overlap between cognitive ability and educational and socioeconomic level, providing evidence of the overlapping biological associations on the neurological level.

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Author contributions

XS developed the design of the study and conducted the analyses. XS, AMM, and HCW drafted the manuscript. AMM and HCW supervised and contributed to the design of the study. IJD, SRC, SJR, DMH, SML, and MEB were involved in overseeing analysis methodology and editing the paper. MJA was involved in curating the data. UK Biobank collected all data and was involved in the preprocessing of imaging data. All authors discussed and commented on the manuscript.

A preprint of the manuscript was uploaded and open for access on biorxiv. It can be found in the URL: https://www.biorxiv.org/content/early/2017/07/15/164053.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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Table 1. The significant associations between the connections of networks of interest and cognitive performance (verbal-numerical reasoning) and educational attainment. The values of connections were transformed into strength before conducting the analyses, by multiplying the connection values with the signs of their means. This approach was consistent with ref 28. Mean values and their 95% confident intervals of connections reported here are the values before being transformed into strength.

Verbal-Numerical Reasoning									
Type	**Connections**	**Beta**	**Standard error**	**t.value**	**p**	**pcorrected**	**Mean value of connection**	**95% confident interval of value of connection**	
inter-hemisphere	**left FPN - right FPN**	-0.040	0.016	-2.493	1.27E-02	0.018	1.156	1.127	1.185
	right CON - left CON	-0.063	0.016	-3.923	8.89E-05	6.67E-04	0.379	0.356	0.402
CON - FPN	**left CON - right FPN**	0.034	0.016	-2.106	3.52E-02	0.044	-1.359	-1.387	-1.330
	right CON - left FPN	0.043	0.016	-2.714	6.68E-03	0.011	-2.088	-2.122	-2.054
	left CON - left FPN	0.044	0.016	2.732	6.33E-03	0.011	1.043	1.018	1.067
	right CON - right FPN	0.051	0.016	3.200	1.38E-03	0.005	0.648	0.620	0.676
DMN-related	**left CON - DMN**	0.061	0.016	3.824	1.33E-04	6.67E-04	0.675	0.652	0.698
	right CON - DMN	-0.045	0.016	2.797	5.18E-03	0.011	-0.275	-0.300	-0.250

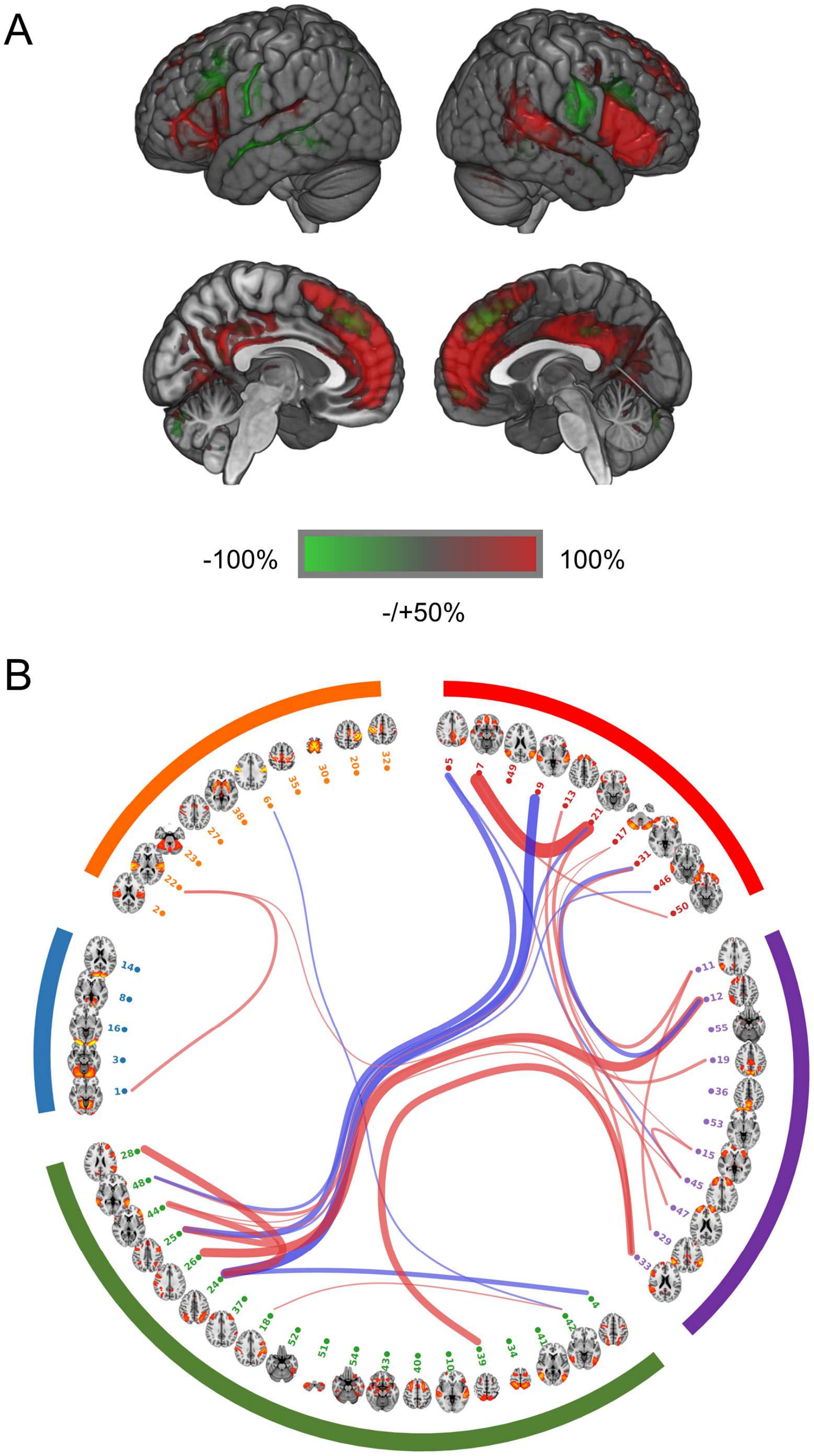
Educational attainment									
Type	**Connections**	**Beta**	**Standard error**	**t.value**	**p**	**pcorrected**	**Mean value of connection**	**95% CI of value of connection**	
CON - FPN	**right CON - right FPN**	0.086	0.031	2.736	6.24E-03	0.021	0.648	0.620	0.676
DMN-related	**right FPN - DMN**	0.104	0.031	-3.335	8.59E-04	0.004	-0.710	-0.738	-0.682
	right CON - DMN	-0.149	0.031	4.761	1.99E-06	1.99E-05	-0.275	-0.300	-0.250

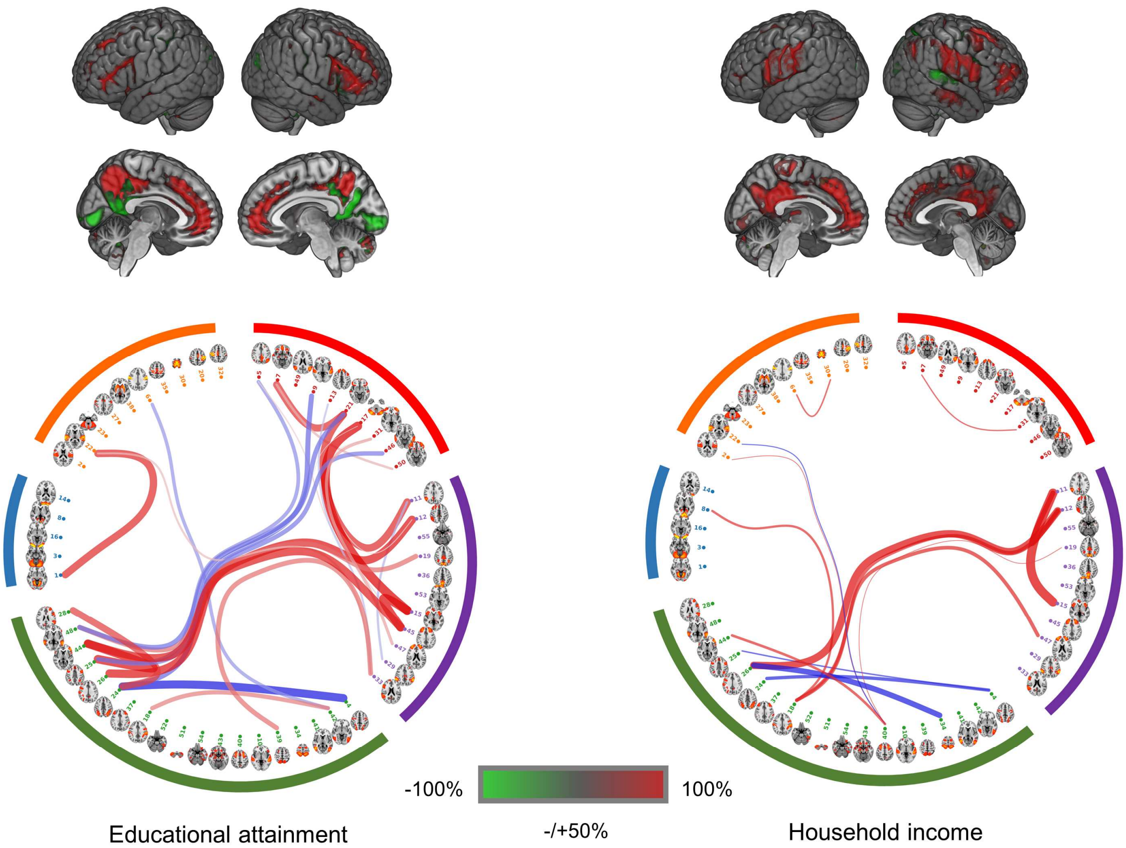
Figure legends

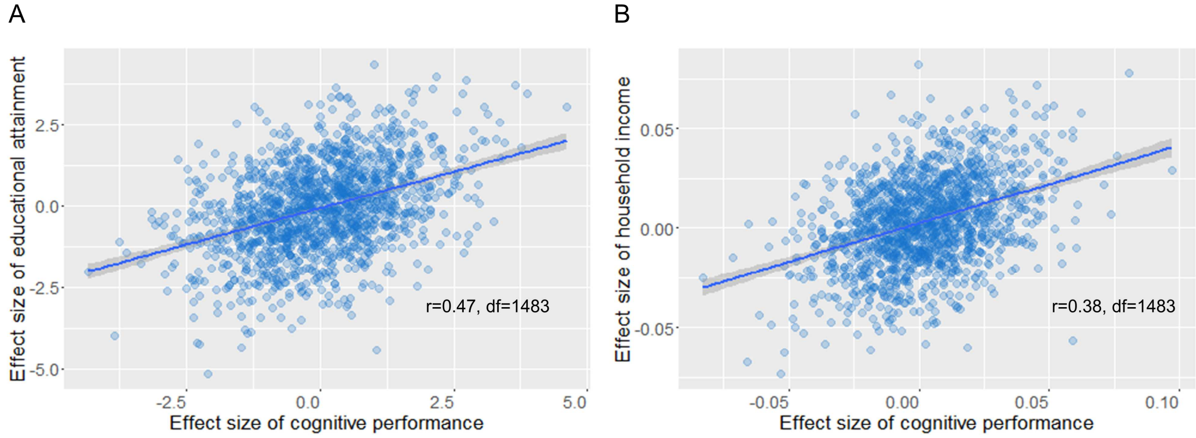
Figure 1. (A) Connections that showed significant associations with cognitive performance. The ICA components were clustered into five categories according to the group-mean full correlation matrix for better illustration and interpretation of the results. This clustering gives a data-driven, gross overview of the structure of the components, consistent with previous studies (ref 26 and 30). The clusters roughly represent the resting state networks (RSNs) of: default mode network (red), extended default mode network and cingulo-opercular network (purple), executive control and attention network (green), visual network (blue) and sensorimotor network (orange). Red lines are the connections where strength was positively associated with cognitive performance; blue lines denote negative associations with cognitive performance. The width of lines indicates the effect sizes of the associations between connection strength and cognitive performance (bigger width indicates a larger absolute effect size). The significant connections were mostly involved in the categories of default mode network, executive control/attention network and cingulo-opercular network. (B) The spatial map of regions involved with connections in (A). The spatial maps for the ICA nodes that involved in the significant connections were multiplied by their effect sizes, then the spatial map in (B) was generated by summing up the weighted maps. To better illustrate the regions involving in significant connections, a threshold of 50% of the highest intensity was applied, so the regions with intensity higher than the threshold would show on the map.

Figure 2. The connections that showed significant associations with educational attainment and household income. Red lines are the connections of which the strength was positively associated with cognitive performance, and the blue lines are the ones having negative associations. The width of lines indicates the effect sizes of the strength of the connections, see the legend of Figure 1. The categorisation of components of brain regions in the circular brain network illustration is identical with Figure 1. Again like Figure 1, A threshold of 50% of the highest value was applied for better illustration of the projection of brain regions on MNI template.

Figure 3. Correlations of the effect sizes of (A) cognitive performance and educational attainment and (B) cognitive performance and household income on whole-brain connections using 55*55 partial correlation matrix as the proxy. Regression line with 95% confident intervals (shaded) are shown.


A
-100%
100%
-/+50%
B


-100%
100%
-/+50%
Educational attainment
Household income


A
Effect size of educational attainment
2.5
0.0
-2.5
-5.0
-2.5
0.0
2.5
5.0
Effect size of cognitive performance
r=0.47, df=1483
B
Effect size of household income
0.05
0.00
-0.05
-0.05
0.00
0.05
0.10
Effect size of cognitive performance
r=0.38, df=1483

Resting-State Connectivity and Its Association With Cognitive Performance, Educational Attainment, and Household Income in UK Biobank

Supplementary Information

Supplementary Methods

Participants

The UK Biobank covers an age range from 40 to 70 at the initial visit, and by the time of the imaging assessment, the age range was from 45 to 75, because the imaging assessment took place after the initial visit. The imaging sample was selected within the overall sample for predominantly healthy participants to achieve a selection of population-based sample. The UK Biobank sample chose mainly white people with European ancestry. The education level was comparatively high, with a proportion of 53.15% received college or university level degree.

Clustering of 55*55 matrix

The clustering for the whole-brain analyses on 55*55 connectivity matrix was for better illustration, using hierarchical clustering approach described in: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0076315. The number of cluster was user-defined as n=5.

Educational attainment and household income

For educational attainment, participants could choose at least one of the following options: College or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications, none of the above, and prefer not to answer.

For household income, available choices were: <£18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, >£100,000, do not know and prefer not to answer. An ordinal variable from 1 to 5 was created to determine the level of household income (<£18,000 as 1, >£100,000 as 5).

PCA analysis for cognitive performance, educational attainment and household income

As the results in the main text showed that the regions involved in the three traits were highly overlapping, we have conducted a PCA analysis to extract the first unrotated latent component of the three traits, and used the scores for the factor to test the resting-state-network associations with the common variance of all three traits.

PCA was conducted using princomp in R (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/princomp.html). Results are shown in supplementary results and Figure S5.

Permutation test

As we now have an updated sample of 7,144 people (from the latest data release), we have now additionally conducted two further sets of analyses to validate our results.

First we performed permutation test on half-sized sample (N=3,572) and tested the distributions of the p values for the significant connections found in 55*55 matrix described in our initial findings. After 1,000 times of randomly selecting half of our sample, conducting analyses on them, we found that the distributions of p values for over 90% of the significant connections found in our initial results were lower, compared with the mean p value for the rest of connections (Figure S7-S9).

Second, another permutation test was performed to test whether the results found in a training subsample can predict the results in a separate testing sample. We cut the sample in halves, and used the first half as a training dataset and the second half as a testing dataset. We extracted the effect sizes for the 55*55 connectivity matrix acquired from the training sample and applied them on the testing dataset to calculate a neural connectivity score for the trait. And then we used the neural connectivity score to predict the variances for the traits in the testing sample. For instance, we used the effect sizes of cognitive performance in the training sample ($\beta_{training}$), and calculated the sum of βtraining*$Connectivity_{testing}$ as the neural-network score of cognitive performance in the testing sample. We then used this score to predict the cognitive performance, educational attainment and household income in the testing sample. Age, age^2, gender, scanner positions and mean motion were controlled. Likewise permutation tests were conducted to use the neural associations of educational attainment or household income to predict other traits in the testing sample. Results are shown in Figure S10.

Supplementary Results

Phenotypic associations

The mean test performance score for the VNR was 6.92 (SD = 2.15). Age and sex both showed significant associations with VNR score (age: β=-0.07, p=3.50X10-5, sex: β=0.19, p=3.18X10-9; Male=1, Female=0).

In total, 1,801 participants reported having obtained a college/university-level degree (43.29% of the overall sample). The mean age of people with a college/university-level degree was 61.62 (SD=7.49), which was significantly lower than the group without (Mean age=62.65, SD=7.58, t=4.37, p=1.27X10-5). Men reported a significantly higher proportion of college degrees (48.80%) than women (39.73%), χ2=34.8, df=1, p=3.65X10-9. Educational attainment showed positive association with cognitive performance, with age, age2 and sex controlled (β=0.457, p<2X10-16).

The proportion of people who reported having household income at each level is shown in Figure S1. The income band of £31,000 to £51,999 contained the highest proportion (29.98%) of individuals, and the band >£100,000 contained the lowest proportion (6.06%). Both age and sex showed significant associations with household income (age: β=-0.29, p<2X10-16; sex: β=0.20, p=1.04X10-9). Higher household income was associated with better cognitive performance (β=0.167, p<2X10-16), with age, age2, and sex controlled in the model.

PCA analysis of cognitive performance, educational attainment and household income

The first latent component (g) of the three traits explains a major portion of total variance (75.6%), it was heavily loaded on cognitive performance (correlation loadings: cognitive performance: 0.998, educational attainment: 0.261, household income: 0.220).

We have conducted an additional analysis using the first latent component as a predictor and tested the shared component of cognitive performance, educational attainment and household income on the resting-state networks (see supplementary methods). Results are shown in Figure S7. As expected, the regions involved with stronger connections with latent g of the three traits were mainly located in default mode network areas and lateral prefrontal cortex.

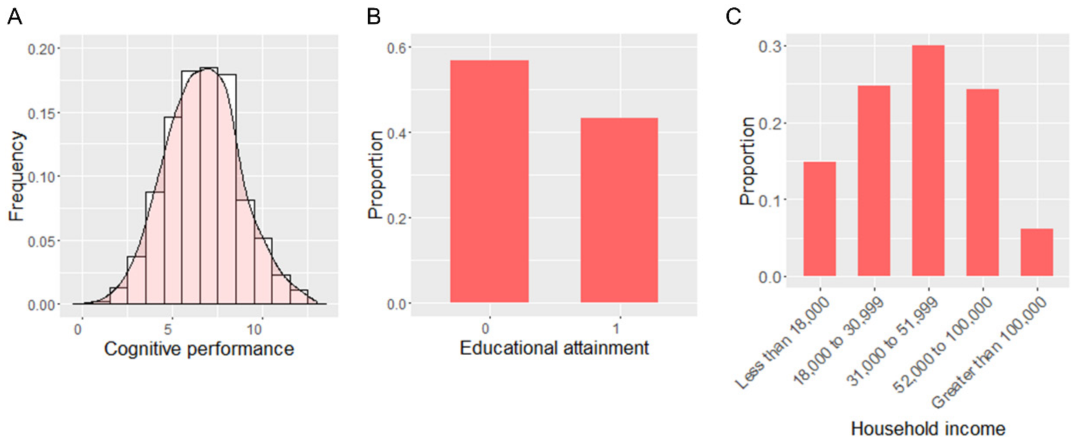


Figure S1. Descriptive statistics of (a) cognitive performance on the verbal-numerical reasoning test; (b) educational attainment (those with [0] and without [1] a college degree; and (c) household income (GBP per annum).

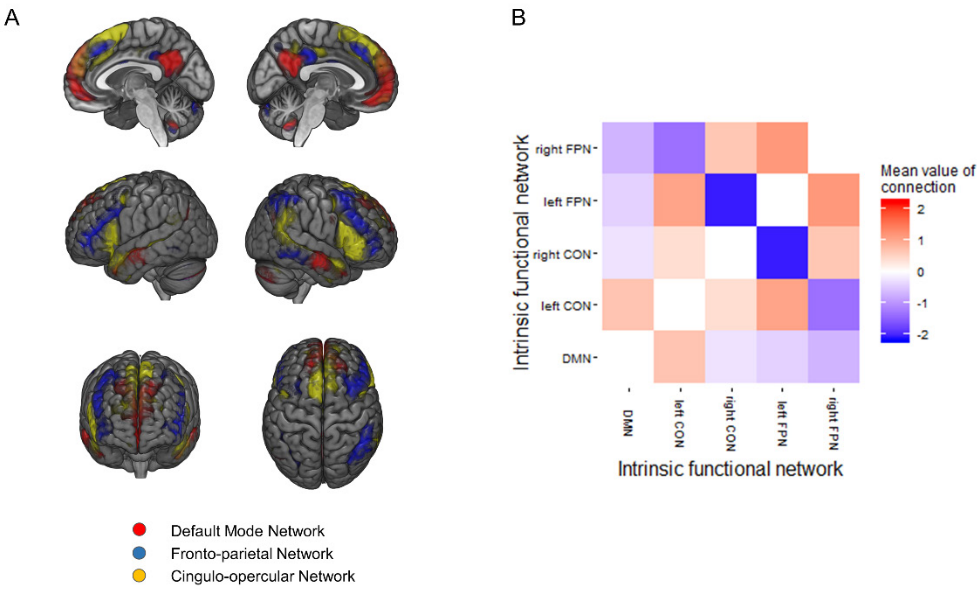


Figure S2. (A) Five intrinsic functional networks selected from the 21 components generated by low-dimension ICA (see Methods, Imaging data). Component 1 was identified as the default mode network (DMN, red). Component 13 and 21 were left and right cingulo-opercular network (CON) respectively (yellow). And finally, component 5 and 6 were identified as right and left fronto-parietal network (FPN, blue). (B) The mean values of couplings of networks of interest. The values are standardised temporal correlation coefficient between networks of interest. A higher absolute value indicates a higher strength, and the sign indicates the directionality of the connection. A negative value means an anti-correlated connection, whilst a positive value indicates a positive connection. Mean values and 95% confident intervals of the connections can be viewed in Table 1.

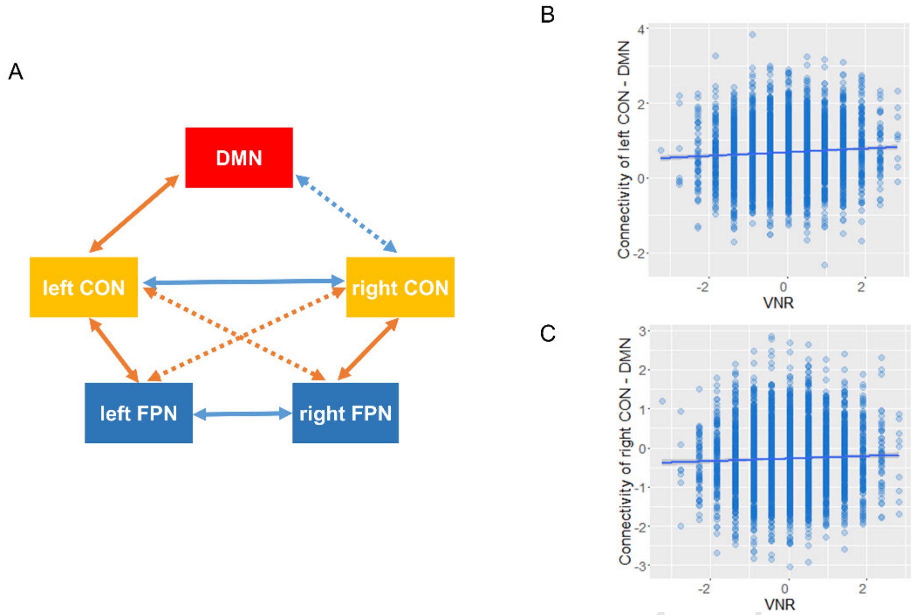


Figure S3. (A) Significant network couplings associated with cognitive performance in verbal-numerical reasoning (absolute β ranged from 0.034 to 0.063, all effect sizes of the significant connections are reported in Table 1). An orange arrow means positive association between cognitive ability with the absolute strength of a connection, whilst a blue arrow indicates decreased absolute strength of a connection with better cognitive performance. Solid arrows are positive connections and dashed ones are negative. An orange arrow reflects positive associations between cognitive ability with the absolute strength of a connection, whilst a blue arrow indicates decreased absolute strength of a connection with better cognitive performance. (B) and (C) represent the association of cognitive performance in verbal-numerical reasoning and the connection between left/right CON (β=0.061 and -0.045 respectively for left/right CON) and DMN (β=-0.045). Y-axis represent the normalised correlation coefficient between temporal modulations of networks. Better cognitive performance was associated with more positive connections between DMN and bilateral CON. The spatial maps of the functional networks can be found in Figure S2.

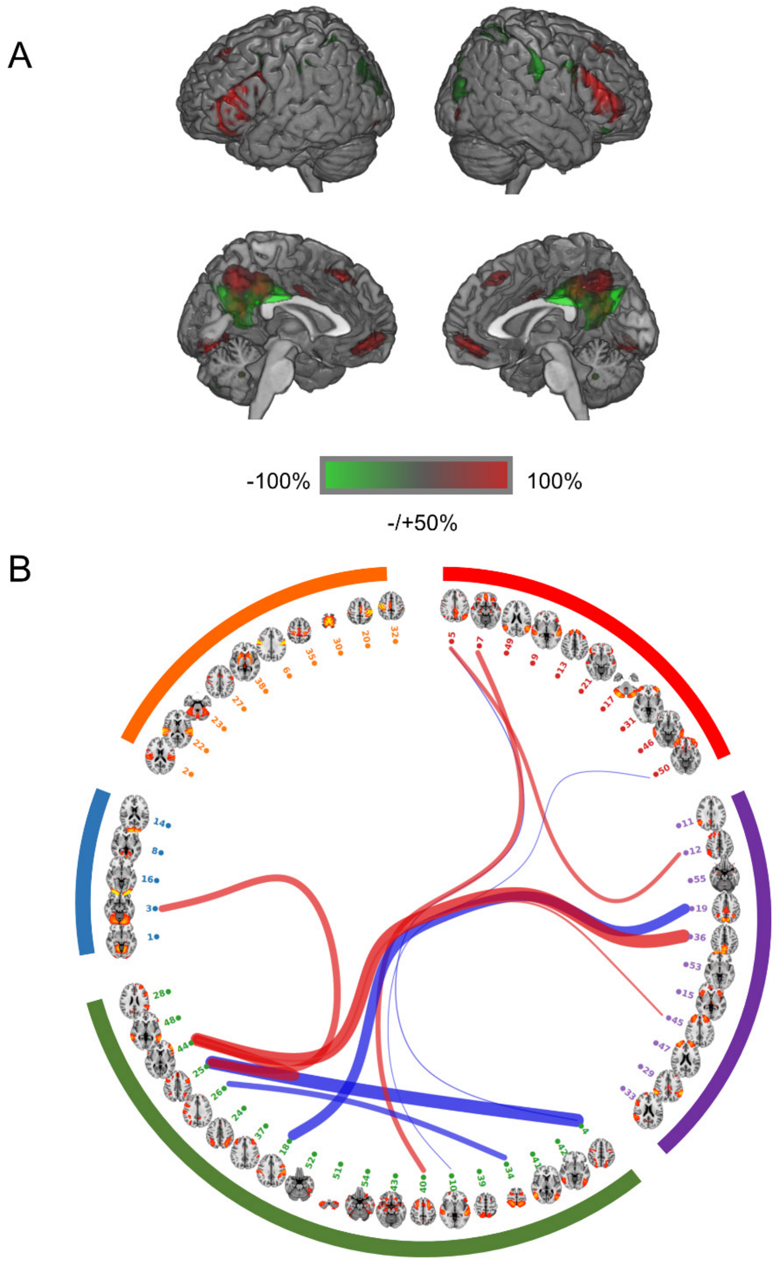


Figure S4. Results for whole-brain analysis of non-binary proxy for educational attainment. Three levels were set, which included: college or university level, A or AS level, and all other levels.

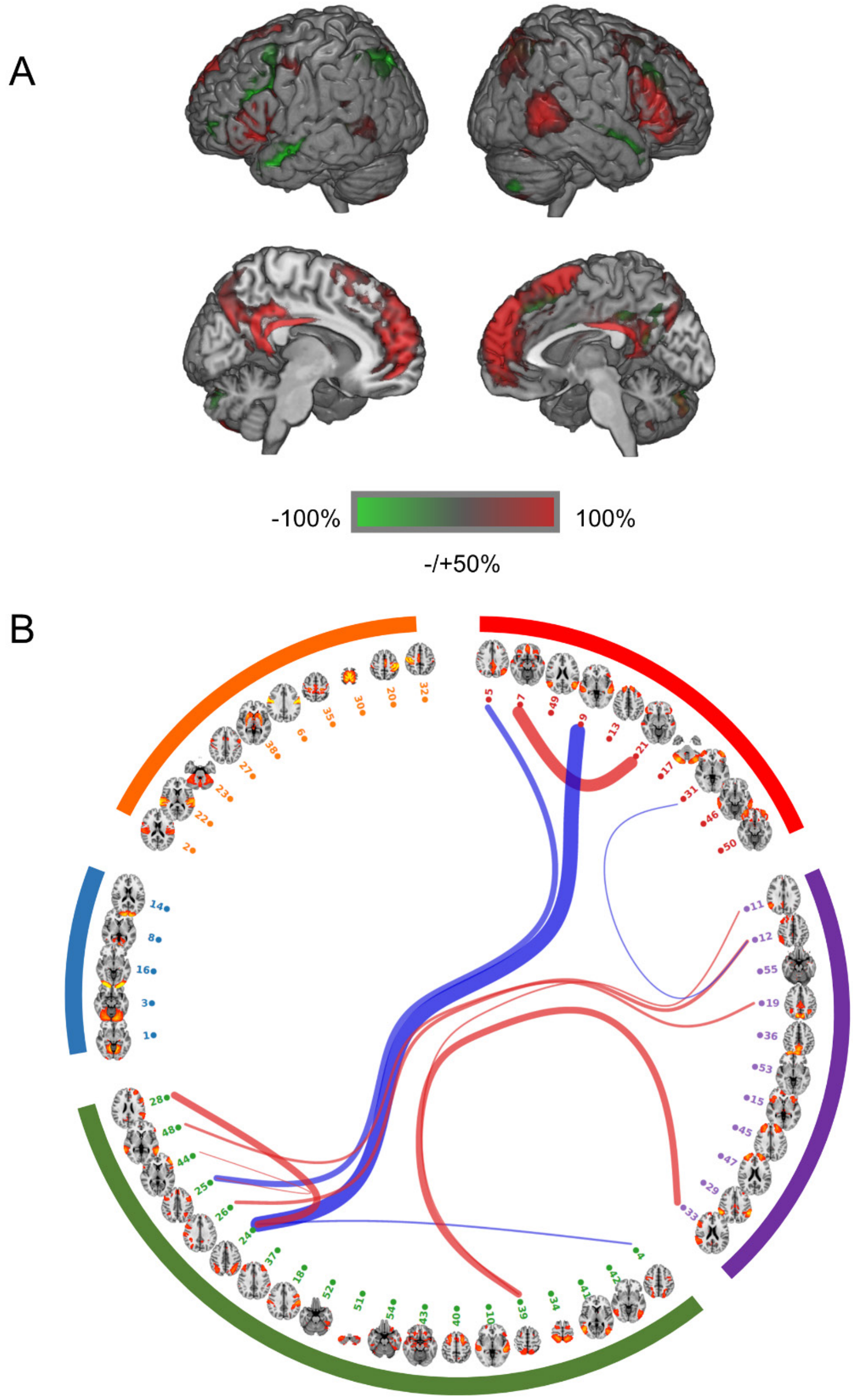
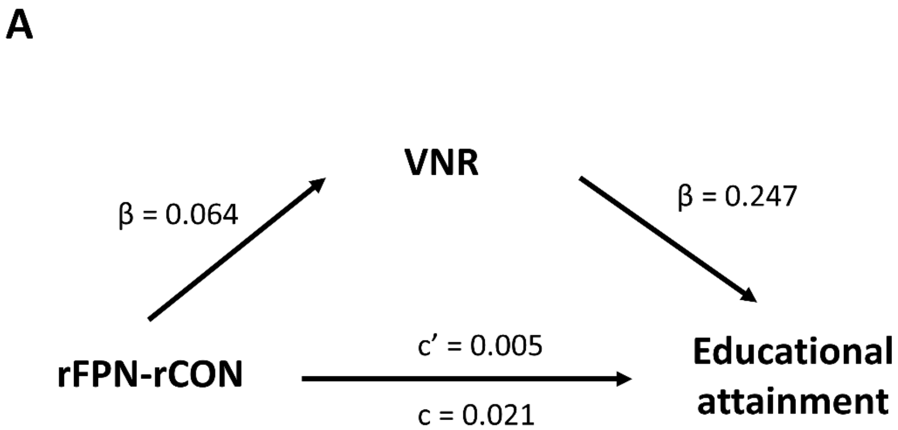


Figure S5. Results for whole brain analysis of the first latent component of cognitive performance (VNR), educational attainment and household income. The first latent component was extracted from unrotated PCA by using princomp in R (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/princomp.html). This component explains 75.6% of total variance. Correlation loadings for the factor are: cognitive performance: 0.998, educational attainment: 0.261, household income: 0.220.



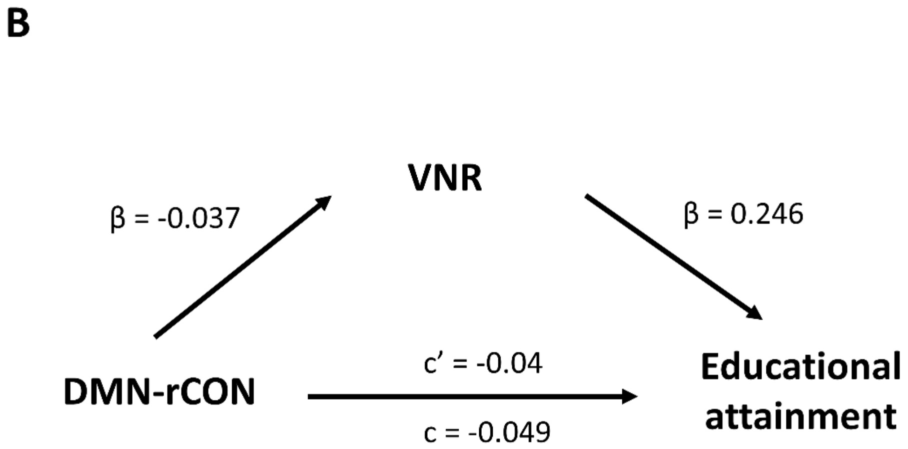


Figure S6. Mediation analysis for NOI results. Network connectivity was set as the predictor, and educational attainment as the dependent variable. Mediator was set as cognitive performance. We tested on two network connections that were significant for both educational attainment and cognitive performance. The association between rFPN-rCON and rCON-DMN connectivity and educational attainment was mediated by cognitive performance (18.4% and 76.2% of direct path mediated by indirect path respectively for each model, CFI = TLI = 1).

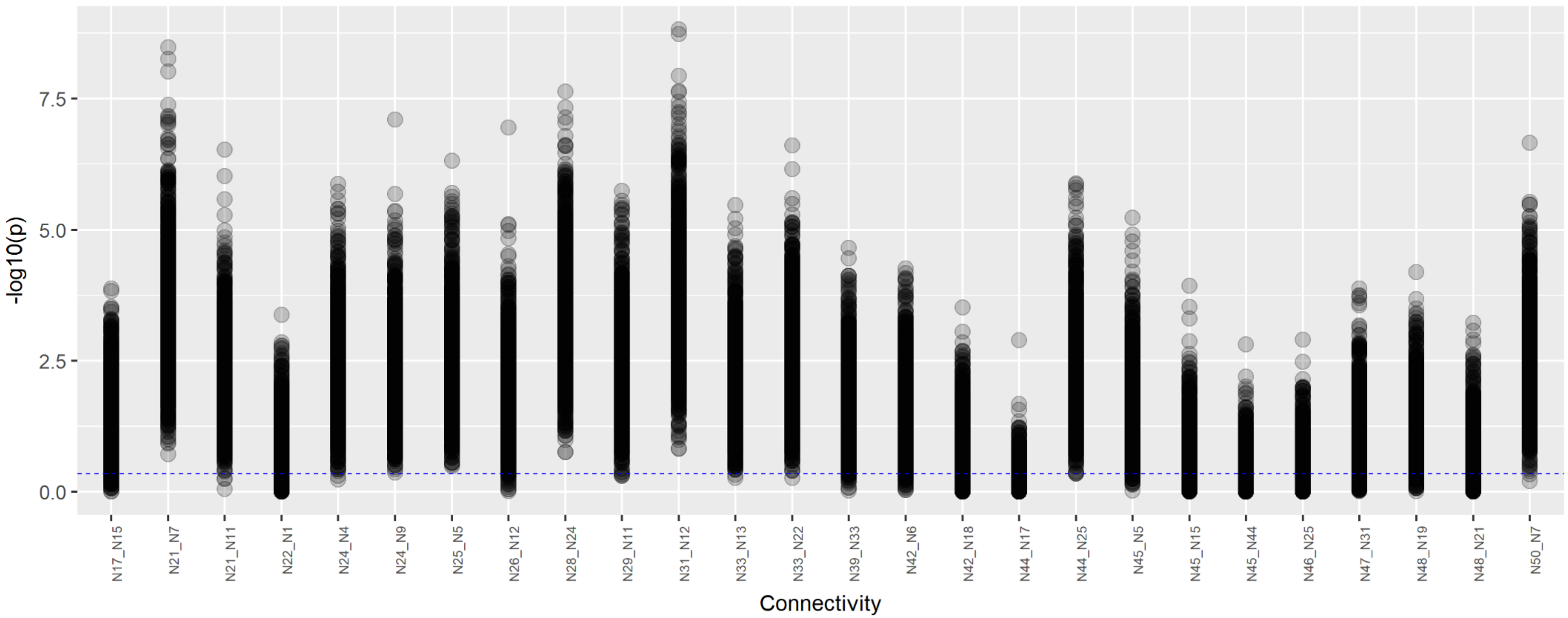


Figure S7. Permutation test on cognitive performance (VNR). X axis shows the connections, and y axis shows the uncorrected p value transformed by -log10 function. T-test was performed on the p-value distributions for each connection that was found associated with VNR to test whether these tested connections have significantly lower p values compared to the non-significant connections in the initial finding. The dashed blue line is the mean uncorrected p value of all other connections. Two connections' p values were not significantly lower than the mean p value of all other connections (N44-N17: $t(999)=18.25$, $p<1E-16$, and N45-N44: $t(999)=6.95$, $p=6.50E-12$). All other connections have lower p values compared to the non-significant ones, which takes up 92.3% of all 26 connections (t-test $p<1E-16$).

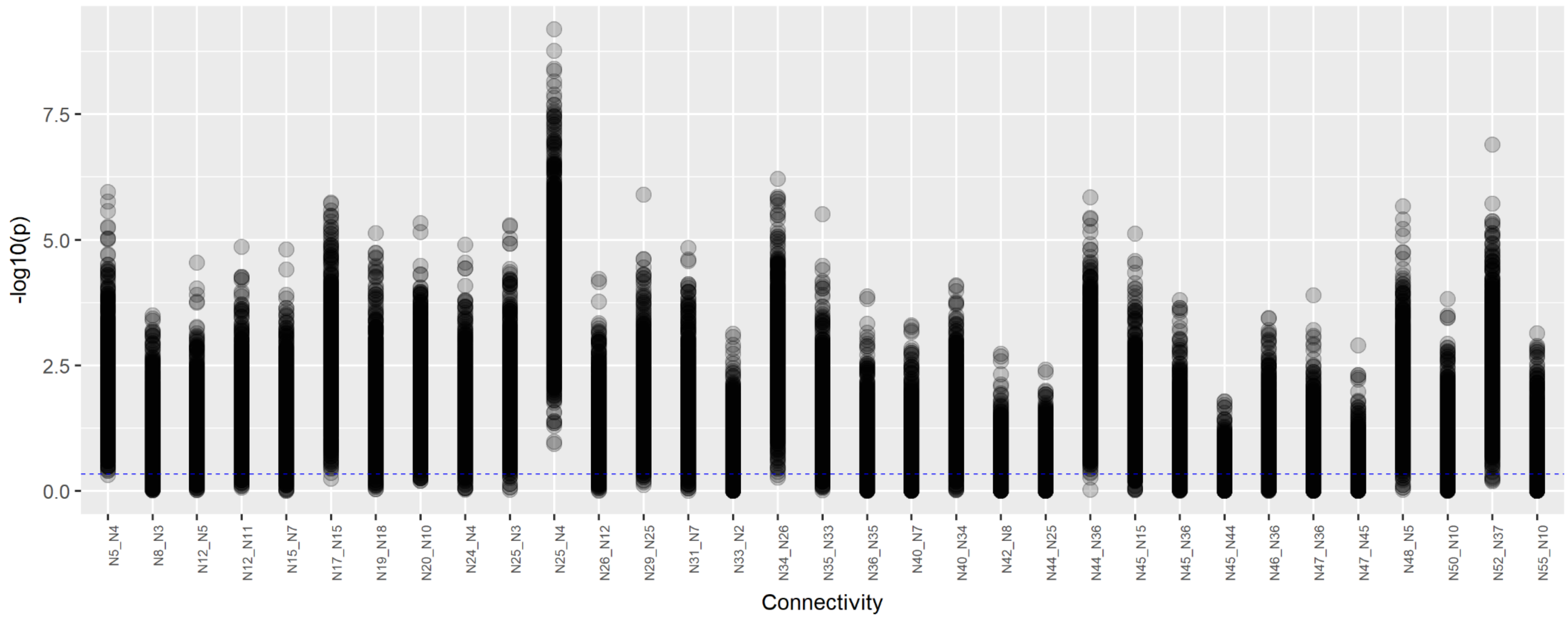


Figure S8. Permutation test on educational attainment. X axis shows the connections, and y axis shows the uncorrected p value transformed by -log10 function. T-test was performed on the p-value distributions for each connection that was found associated with educational attainment to test whether these tested connections have significantly lower p values compared to the non-significant connections in the initial finding. The dashed blue line is the mean uncorrected p value of all other connections. Three connections' p values were not significantly lower than the mean p value of all other connections (N44-N25: $t(999)=1.22$, $p=0.22$, N45-N44: $t(999)=11.55$, $p<1E-16$, and N47-N45: $t(999)=4.98$, $p=7.34E-7$). All other connections have lower p values compared to the non-significant ones, which takes up 90.0% of all 33 connections (t-test $p<1E-16$).

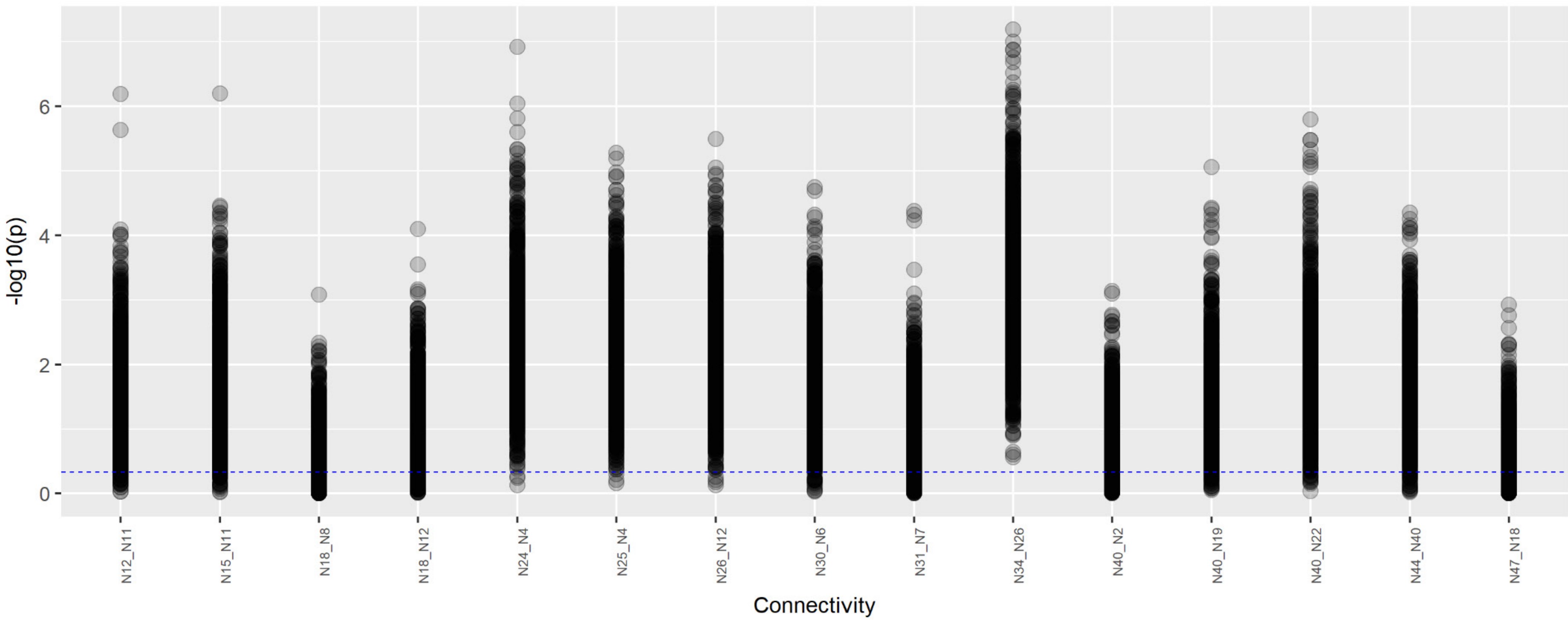
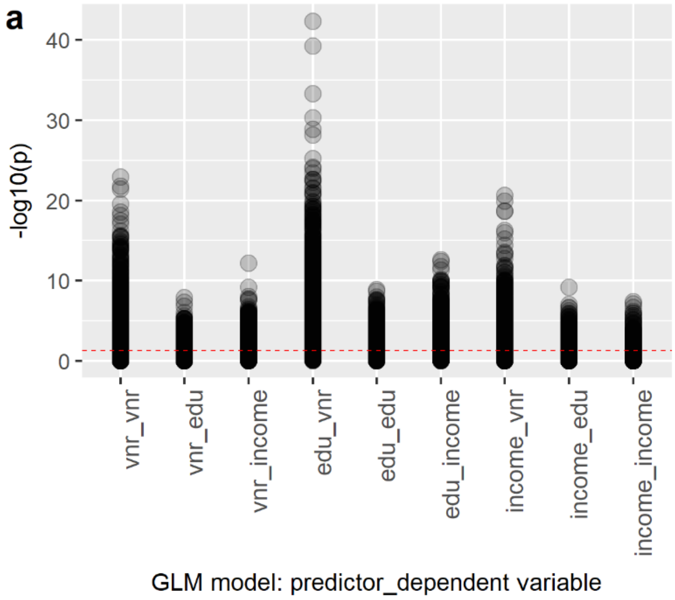


Figure S9. Permutation test on household income. X axis shows the connections, and y axis shows the uncorrected p value transformed by -log10 function. T-test was performed on the p-value distributions for each connection that was found associated with household income to test whether these tested connections have significantly lower p values compared to the non-significant connections in the initial finding. The dashed blue line is the mean uncorrected p value of all other connections. All the connections have lower p values compared to the non-significant ones (t-test $p<4.91E-8$).



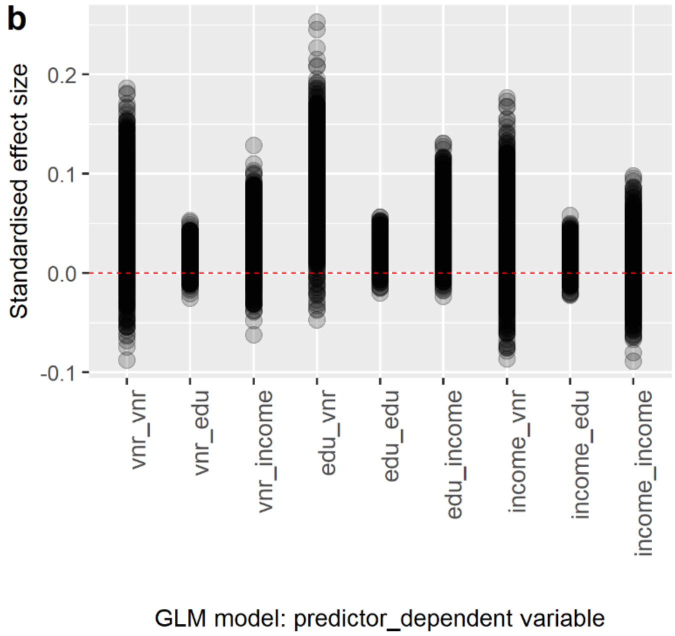


Figure S10. Using the model built by the training sample to predict the traits in the testing sample. The x axis is the models of using predictors derived from training sample to predict the trait as the dependent variable in the testing sample. In panel a, the y axis is the uncorrected p value transformed by -log10. In panel a, the red dashed line is the p=0.05 significance line, as there is no baseline mean p value to compare with like in Figure S6-8. In Figure b, the y axis is the standardised effect size. We also conducted t-test to compare the effect sizes with 0, and all models showed significant difference from 0 (income_income: $p = 0.009$, for all other models: $p < 1 \times 10^{-16}$).

Table S1. Connections that showed significant association with cognitive performance in VNR on 55*55 partial correlation matrix. All reported betas are standardised effect sizes. The regression model was applied to test the association between VNR and absolute strength of connections, which was achieved by multiplying values of connections with the sign of their mean value (see Methods). The spatial maps of the nodes in the table indicated by numbers can be found in Figure 2.

	Beta	Standard error	t.value	p	p.corrected	Valence of connection	95% CI of value of connection	
N17_N15	0.054	0.016	-3.403	6.73E-04	0.038	+	1.215	1.275
N21_N11	0.062	0.016	3.901	9.72E-05	0.014	-	-1.939	-1.881
N21_N7	0.097	0.016	6.140	9.09E-10	0.000	+	3.746	3.829
N22_N1	0.061	0.016	-3.789	1.53E-04	0.018	-	-0.561	-0.510
N24_N4	-0.066	0.016	-4.092	4.37E-05	0.007	-	-1.136	-1.075
N24_N9	-0.083	0.016	5.196	2.14E-07	<0.001	+	0.319	0.363
N25_N5	-0.072	0.016	4.488	7.39E-06	0.002	-	-0.639	-0.579
N26_N12	0.081	0.016	5.036	4.96E-07	0.000	+	3.746	3.829
N28_N24	0.076	0.016	4.737	2.25E-06	0.001	+	0.151	0.206
N29_N11	0.059	0.016	3.671	2.45E-04	0.021	+	0.762	0.830
N31_N12	-0.066	0.016	-4.109	4.06E-05	0.007	+	1.234	1.300
N33_N13	0.060	0.016	-3.751	1.78E-04	0.018	-	-0.702	-0.649
N33_N22	0.055	0.016	3.412	6.52E-04	0.038	+	0.649	0.701
N39_N33	0.074	0.016	-4.580	4.80E-06	0.001	-	-0.561	-0.510
N42_N18	0.055	0.016	3.445	5.77E-04	0.037	+	1.671	1.737
N42_N6	-0.056	0.016	3.516	4.43E-04	0.031	-	-0.594	-0.548
N44_N17	0.054	0.016	3.425	6.21E-04	0.038	+	0.276	0.314
N44_N25	0.071	0.016	4.477	7.78E-06	0.002	+	2.321	2.383
N45_N15	0.059	0.016	3.682	2.34E-04	0.021	+	1.233	1.291
N45_N44	0.055	0.016	-3.494	4.81E-04	0.032	-	-1.264	-1.217
N45_N5	-0.058	0.016	-3.625	2.93E-04	0.024	+	0.026	0.095

	Beta	Standard error	t.value	p	p.corrected	Valence of connection	95% CI of value of connection	
N46_N25	-0.057	0.016	-3.543	4.00E-04	0.030	+	0.002	0.046
N47_N31	0.059	0.016	3.766	1.68E-04	0.018	+	1.096	1.159
N48_N19	0.061	0.016	-3.780	1.59E-04	0.018	-	-0.679	-0.627
N48_N21	-0.061	0.016	-3.804	1.44E-04	0.018	+	0.005	0.053
N50_N7	0.057	0.016	-3.591	3.33E-04	0.026	-	-0.251	-0.213

Table S2. Connections that showed significant association between their absolute strength with educational attainment on the whole brain proxied by 55*55 partial correlation matrix. The spatial maps of the nodes in the table indicated by numbers can be found in Figure 2.

	Beta	Standard error	t.value	p	p.corrected	Valence of connection	95% CI of value of connection	
N5-N4	-0.103	0.031	3.290	1.01E-03	0.045	-	-0.720	-0.660
N8-N3	-0.119	0.031	-3.809	1.42E-04	0.018	+	0.903	0.994
N12-N5	0.132	0.031	-4.201	2.71E-05	0.007	-	-2.111	-2.036
N12-N11	0.106	0.031	3.394	6.94E-04	0.040	+	6.507	6.608
N15-N7	0.122	0.031	3.949	7.96E-05	0.015	+	0.875	0.929
N17-N15	0.121	0.031	-3.905	9.59E-05	0.015	-	-0.825	-0.784
N19-N18	-0.136	0.031	4.338	1.47E-05	0.005	-	-0.747	-0.689
N20-N10	-0.109	0.031	3.488	4.91E-04	0.038	-	-0.443	-0.399
N24-N4	-0.108	0.031	-3.428	6.15E-04	0.038	+	0.588	0.651
N25-N3	0.137	0.031	-4.355	1.36E-05	0.005	-	-0.264	-0.223
N25-N4	-0.161	0.031	-5.150	2.73E-07	<0.001	+	0.995	1.059
N26-N12	0.108	0.031	3.457	5.51E-04	0.038	+	3.746	3.829
N29-N25	0.108	0.031	-3.440	5.88E-04	0.038	+	0.180	0.241
N31-N7	0.125	0.031	-3.995	6.57E-05	0.014	-	-1.939	-1.881
N33-N2	-0.103	0.031	-3.294	9.96E-04	0.045	+	0.257	0.310
N34-N26	-0.133	0.031	-4.254	2.14E-05	0.006	+	0.320	0.378
N35-N33	0.108	0.031	-3.452	5.63E-04	0.038	-	-0.075	-0.035
N36-N35	0.105	0.031	-3.363	7.79E-04	0.041	-	-0.636	-0.596
N40-N7	0.118	0.031	-3.761	1.72E-04	0.020	-	-0.694	-0.648
N40-N34	0.122	0.031	-3.888	1.03E-04	0.015	-	-0.479	-0.429
N42-N8	-0.108	0.031	3.439	5.89E-04	0.038	-	-0.756	-0.699
N44-N25	0.112	0.031	3.589	3.35E-04	0.029	+	2.321	2.383

	Beta	Standard error	t.value	p	p.corrected	Valence of connection	95% CI of value of connection	
N44-N36	0.139	0.031	-4.431	9.61E-06	0.005	-	-1.469	-1.424
N45-N15	0.117	0.031	3.717	2.05E-04	0.022	+	1.233	1.291
N45-N36	0.105	0.031	3.348	8.20E-04	0.041	+	0.617	0.662
N45-N44	0.105	0.031	-3.403	6.74E-04	0.040	-	-1.264	-1.217
N46-N36	0.110	0.031	-3.509	4.54E-04	0.037	-	-0.935	-0.890
N47-N36	0.105	0.031	3.358	7.93E-04	0.041	+	0.721	0.766
N47-N45	0.110	0.031	3.590	3.35E-04	0.029	+	2.071	2.130
N48-N5	-0.114	0.031	3.641	2.75E-04	0.027	-	-0.123	-0.055
N50-N10	-0.121	0.031	3.861	1.15E-04	0.015	-	-0.606	-0.569
N52-N37	0.104	0.031	3.343	8.37E-04	0.041	+	0.303	0.344
N55-N10	-0.105	0.031	3.337	8.53E-04	0.041	-	-0.063	-0.034

Table S3. Connections that showed significant association between their absolute strength with household income on the whole brain proxied by 55*55 partial correlation matrix. The significant connections presented in the table is identical with those connections shown in Figure 2.

	Beta	Standard error	t.value	p	p.corrected	Valence of connection	95% CI of value of connection	
N12_N11	0.072	0.017	4.208	2.64E-05	0.010	+	6.507	6.608
N15_N11	0.082	0.017	-4.806	1.60E-06	0.002	-	-1.246	-1.185
N18_N8	0.064	0.017	3.720	2.02E-04	0.033	+	0.216	0.267
N18_N12	0.067	0.017	-3.909	9.42E-05	0.020	-	-2.099	-2.035
N24_N4	-0.067	0.017	-3.908	9.49E-05	0.020	+	0.588	0.651
N25_N4	-0.062	0.017	-3.629	2.88E-04	0.039	+	0.995	1.059
N26_N12	0.078	0.017	4.531	6.04E-06	0.004	+	3.746	3.829
N30_N6	0.062	0.017	3.634	2.83E-04	0.039	+	0.350	0.411
N31_N7	0.062	0.017	-3.603	3.19E-04	0.039	-	-1.939	-1.881
N34_N26	-0.073	0.017	-4.269	2.01E-05	0.010	+	0.320	0.378
N40_N2	0.060	0.017	-3.526	4.27E-04	0.042	-	-1.806	-1.752
N40_N19	0.060	0.017	-3.539	4.06E-04	0.042	-	-1.136	-1.075
N40_N22	-0.061	0.017	3.554	3.84E-04	0.042	-	-0.548	-0.506
N44_N40	0.065	0.017	-3.812	1.40E-04	0.026	-	-0.509	-0.460
N47_N18	0.068	0.017	-3.967	7.42E-05	0.020	-	-0.724	-0.679

Table S4. Regions involved in the significant connections of VNR. The regions were extracted using the "result" function of SPM (http://www.fil.ion.ucl.ac.uk/spm/). Clusters that were above 50% of the highest global intensity and cluster size above 20 are reported in the following tables. The coordinates and AAL labels indicate the peak of the reported cluster.

Positive connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	-22, -74, -26	Cerebelum_Crus1_L	2804	6.4319
2	36, -72, -40	Cerebelum_Crus2_R	2661	4.765
3	-12, -48, -42	Cerebelum_9_L	159	3.0327
4	50, 4, -38	Temporal_Inf_R	157	3.0399
5	2, -68, -32	Vermis_8	36	2.5446
6	56, 34, 0	Frontal_Inf_Tri_R	35023	6.9587
7	-48, -54, -12	Temporal_Inf_L	313	2.8549
8	26, -20, -14	Hippocampus_R	58	3.2229
9	10, 0, 14	Caudate_R	78	3.1414
10	-10, -4, 16	Caudate_L	35	2.8065
11	4, -20, 8	Thalamus_R	29	2.6283
12	-40, -46, 40	Parietal_Inf_L	713	3.1276
13	-24, -10, 50	Frontal_Sup_L	147	2.5947
14	34, -2, 60	Frontal_Mid_R	54	2.053

Negative connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	32, -70, -48	Cerebelum_7b_R	351	-3.5296
2	8, -74, -24	Cerebelum_Crus1_R	1982	-3.4538
3	-2, -52, -34	Cerebelum_9_L	225	-2.4617
4	-22, -34, -42	Cerebelum_10_L	56	-2.3538
5	48, -60, -8	Temporal_Inf_R	2456	-3.9686
6	-28, -74, 22	Occipital_Mid_L	8857	-8.2862
7	30, -64, -28	Cerebelum_6_R	147	-2.8812
8	-46, 14, -14	Temporal_Pole_Sup_L	26	-1.8379
9	-8, 38, -12	Frontal_Med_Orb_L	275	-2.3001
10	-30, 26, -2	Insula_L	988	-3.4967
11	34, 38, -8	Frontal_Inf_Orb_R	144	-3.0886
12	32, 26, -2	Insula_R	260	-3.2563
16	-50, -12, 30	Postcentral_L	6311	-4.4245
17	26, 52, -2	Frontal_Mid_R	338	-2.4291
19	32, -72, 22	Occipital_Mid_R	3881	-7.9954
22	-10, -40, 34	Cingulum_Mid_L	1340	-3.8093

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
23	-8, 0, 12	Caudate_L	51	-2.1585
24	-34, -32, 20	Insula_L	20	-1.757
25	36, -30, 18	Insula_R	23	-1.7716
26	6, 4, 56	Supp_Motor_Area_R	71	-2.3897
27	-4, 6, 54	Supp_Motor_Area_L	31	-1.6887
28	12, -32, 66	Paracentral_Lobule_R	32	-1.8698

Table S5. Regions involved in the significant connections of educational attainment. The coordinates and AAL labels indicate the peak of the reported cluster.

Positive connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	12, -46, -44	Cerebelum_9_R	311	8.8438
2	-38, -66, -42	Cerebelum_Crus2_L	3413	11.1
3	-2, -68, -34	Vermis_8	29	4.7242
4	2, -58, -24	Vermis_6	22	5.1606
5	58, -6, -14	Temporal_Mid_R	402	8.8827
6	-26, -36, -16	Fusiform_L	75	6.8778
7	-24, -20, -16	Hippocampus_L	55	7.7283
8	0, -58, 44	Precuneus_L	13050	15.5606
9	22, 28, 46	Frontal_Sup_R	8148	14.3976
10	-20, 30, 38	Frontal_Mid_L	6549	14.9328
11	-32, 36, -10	Frontal_Inf_Orb_L	421	10.9456
12	-60, -12, -10	Temporal_Mid_L	212	7.2928
13	-54, -46, -12	Temporal_Inf_L	55	6.1464
14	-20, -84, -10	Fusiform_L	739	6.1887
15	56, -40, -10	Temporal_Mid_R	40	4.8633
16	24, -76, -6	Lingual_R	187	6.9006
17	-8, 4, 6	Caudate_L	40	7.5075
18	8, 6, 4	Caudate_R	73	7.6276
19	-48, -24, 6	Temporal_Sup_L	56	5.9954
20	36, -84, 10	Occipital_Mid_R	25	4.1809
21	-46, -48, 12	Temporal_Mid_L	26	4.5143
22	50, -44, 26	SupraMarginal_R	1413	6.1332
23	34, -26, 18	Insula_R	37	5.3353
24	30, -74, 20	Occipital_Mid_R	26	4.8628
25	38, -14, 20	Insula_R	20	5.6089
26	-34, -18, 42	Postcentral_L	189	7.0578
27	-50, -40, 46	Parietal_Inf_L	343	5.4355
28	-16, -4, 68	Frontal_Sup_L	40	5.1036

Negative connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	-10, -72, -26	Cerebelum_Crus1_L	453	-5.7127
2	34, -70, -48	Cerebelum_7b_R	77	-5.1072
3	-16, -42, -46	Cerebelum_9_L	109	-6.2768
4	18, -42, -46	Cerebelum_9_R	114	-7.2587
5	10, -84, -38	Cerebelum_Crus2_R	60	-4.8257
6	-2, -52, -34	Cerebelum_9_L	78	-6.9646
7	10, -74, -24	Cerebelum_6_R	27	-4.779
8	-16, -58, 16	Precuneus_L	15001	-15.7718
9	24, -20, -16	Hippocampus_R	43	-4.5335
10	-22, -22, -16	Hippocampus_L	25	-4.972
11	56, -4, -18	Temporal_Mid_R	110	-5.2959
12	-34, 36, -12	Frontal_Inf_Orb_L	111	-5.2593
13	32, 38, -8	Frontal_Inf_Orb_R	851	-6.4684
14	50, -58, -6	Temporal_Inf_R	366	-6.3365
15	-40, -66, -6	Occipital_Inf_L	689	-6.7649
16	8, 52, -10	Frontal_Med_Orb_R	35	-4.3472
17	-10, 46, -6	Frontal_Med_Orb_L	30	-4.1374
18	40, -18, 0	Insula_R	22	-4.7318
19	38, 0, 14	Insula_R	35	-5.385
20	-46, -22, 20	Rolandic_Oper_L	111	-5.0322
21	-38, -4, 16	Insula_L	38	-7.1293
22	60, -26, 32	SupraMarginal_R	106	-4.2938
23	50, 4, 34	Precentral_R	151	-4.4223
24	-20, 28, 38	Frontal_Sup_L	144	-5.3051
25	-38, -24, 60	Precentral_L	373	-7.4667
26	-26, -8, 48	Precentral_L	89	-4.6457

Table S6. Regions involved in the significant connections of household income. The coordinates and AAL labels indicate the peak of the reported cluster.

Positive connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	24, 26, 50	Frontal_Sup_R	21182	5.4614
2	12, -72, -48	Cerebelum_8_R	394	2.7072
3	64, -16, -16	Temporal_Mid_R	1409	3.2367
4	42, 18, -36	Temporal_Pole_Mid_R	41	1.8175
5	54, 10, -32	Temporal_Pole_Mid_R	21	2.0982
6	28, -70, -24	Cerebelum_6_R	182	2.1569
7	-16, -62, -22	Cerebelum_6_L	56	2.2845
8	10, 44, -20	Rectus_R	35	2.7192
9	40, -2, 16	Insula_R	7530	5.667
10	-38, -4, 16	Insula_L	6699	6.2029
11	-42, -44, -14	Temporal_Inf_L	38	1.8629
12	-24, 42, -14	Frontal_Sup_Orb_L	116	2.5622
13	-38, 48, 2	Frontal_Mid_L	1066	2.6366
14	-46, -68, 8	Temporal_Mid_L	381	2.5717
15	-10, -16, 10	Thalamus_L	121	2.7542

Negative connections

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
1	-28, -70, -50	Cerebelum_8_L	89	-1.7068
2	-14, -52, -48	Cerebelum_9_L	20	-1.5
3	-6, -74, -40	Cerebelum_7b_L	147	-1.8434
4	22, -38, -44	Cerebelum_10_R	34	-1.7134
5	-20, -36, -44	Cerebelum_10_L	31	-1.6446
6	6, -76, -34	Cerebelum_Crus2_R	42	-1.6713
7	-2, -52, -34	Cerebelum_9_L	33	-1.7678
8	-40, -72, -28	Cerebelum_Crus1_L	29	-1.5027
9	-28, -62, -30	Cerebelum_6_L	52	-1.994
10	30, -64, -28	Cerebelum_6_R	21	-1.5615
11	32, -46, -8	Fusiform_R	227	-2.5744
12	52, -16, 6	Temporal_Sup_R	1372	-2.9145
13	44, -56, -6	Temporal_Inf_R	270	-2.3303
14	-40, -32, 10	Temporal_Sup_L	922	-3.1724
15	34, 36, -10	Frontal_Inf_Orb_R	43	-1.6368
16	-28, -60, -8	Fusiform_L	165	-2.5173
17	-40, -66, -6	Occipital_Inf_L	319	-2.3311

No	Coordinate of peak region	AAL label	Number of voxels	Intensity of peak region
18	32, 28, 0	Insula_R	39	-1.5766
19	-28, -74, 22	Occipital_Mid_L	3066	-5.032
20	32, -70, 24	Occipital_Mid_R	4320	-5.2122
21	46, 6, 24	Frontal_Inf_Oper_R	793	-2.1462
22	-34, 8, 28	Frontal_Inf_Oper_L	413	-1.8625
23	8, 16, 50	Supp_Motor_Area_R	58	-1.5919
24	-24, -4, 50	Frontal_Mid_L	707	-2.2576
25	-14, -42, 48	Cingulum_Mid_L	20	-1.436
26	16, -40, 48	Paracentral_Lobule_R	33	-1.5304
27	-6, 16, 48	Supp_Motor_Area_L	29	-1.5881

Table S7. Network-of-interest (NOI) results for cognitive performance (VNR) and educational attainment. The significant between-network connections were shown in the results below.

VNR									
Type	Connections	Beta	Std	t.value	p	$p_{corrected}$	Mean value of connection	95% CI of value of connection	
inter-hemisphere	left FPN - right FPN	-0.040	0.016	-2.493	1.27E-02	0.018	1.156	1.127	1.185
	right CON - left CON	-0.063	0.016	-3.923	8.89E-05	6.67E-04	0.379	0.356	0.402
CON - FPN	left CON - right FPN	0.034	0.016	-2.106	3.52E-02	0.044	-1.359	-1.387	-1.330
	right CON - left FPN	0.043	0.016	-2.714	6.68E-03	0.011	-2.088	-2.122	-2.054
	left CON - left FPN	0.044	0.016	2.732	6.33E-03	0.011	1.043	1.018	1.067
	right CON - right FPN	0.051	0.016	3.200	1.38E-03	0.005	0.648	0.620	0.676
DMN-related	left CON - DMN	0.061	0.016	3.824	1.33E-04	6.67E-04	0.675	0.652	0.698
	right CON - DMN	-0.045	0.016	2.797	5.18E-03	0.011	-0.275	-0.300	-0.250

EDUCATION									
Type	Connections	Beta	Std	t.value	p	$p_{corrected}$	Mean value of connection	95% CI of value of connection	
CON - FPN	right CON - right FPN	0.086	0.031	2.736	6.24E-03	0.021	0.648	0.620	0.676
DMN-related	right FPN - DMN	0.104	0.031	-3.335	8.59E-04	0.004	-0.710	-0.738	-0.682
	right CON - DMN	-0.149	0.031	4.761	1.99E-06	1.99E-05	-0.275	-0.300	-0.250

Table S7. Correlation matrix between average motion during resting-state assessment, first four genetic principal components, cognitive performance (VNR), educational attainment and household income. Motions and genetic principal components showed very weak correlations with VNR, educational attainment and household income.

	Age	Sex	Motion	VNR	Edu	Income
Age	1	0.085	0.155	-0.061	-0.021	-0.28
Sex	0.085	1	0.147	0.081	0.071	0.079
Motion	0.155	0.147	1	-0.085	-0.094	-0.113
VNR	-0.061	0.081	-0.085	1	0.257	0.202
Edu	-0.021	0.071	-0.094	0.257	1	0.237
Income	-0.28	0.079	-0.113	0.202	0.237	1

Table S8. Replication analyses on the (1) unrelated sample, which related people were removed (N=3,253), and (2) updated unrelated sample (N=7,144). Three connections turned null in both unrelated 4k sample and unrelated 7k sample, which takes up 4.05% of 74 significant connections found in the main results. None of the significant connections showed opposite direction of effect in the additional analyses.

		Main model			**Unrelated people (N~=4k)**		**Unrelated people (N~=7k)**	
	Connection	Beta (std)	$P_{uncorrected}$	$P_{corrected}$	Beta (std)	$P_{uncorrected}$	Beta (std)	$P_{uncorrected}$
VNR	N17_N15	0.054 (0.016)	6.73E-04	3.85E-02	0.053 (0.018)	3.36E-03	0.049 (0.012)	7.30E-05
	N21_N7	0.097 (0.016)	9.09E-10	1.35E-06	0.09 (0.018)	5.38E-07	0.074 (0.012)	2.71E-09
	N21_N11	0.062 (0.016)	9.72E-05	1.44E-02	0.067 (0.018)	2.28E-04	0.058 (0.012)	3.14E-06
	N22_N1	0.061 (0.016)	1.53E-04	1.77E-02	0.051 (0.018)	4.99E-03	0.025 (0.012)	4.66E-02
	N24_N4	-0.066 (0.016)	4.37E-05	7.21E-03	-0.064 (0.018)	4.36E-04	-0.052 (0.013)	3.71E-05
	N24_N9	-0.083 (0.016)	2.14E-07	1.59E-04	-0.073 (0.018)	6.33E-05	-0.059 (0.012)	2.45E-06
	N25_N5	-0.072 (0.016)	7.39E-06	1.65E-03	-0.084 (0.018)	3.57E-06	-0.057 (0.012)	3.75E-06
	N26_N12	0.081 (0.016)	4.96E-07	2.45E-04	0.061 (0.018)	7.47E-04	0.052 (0.012)	2.57E-05
	N28_N24	0.076 (0.016)	2.25E-06	8.35E-04	0.081 (0.018)	1.01E-05	0.074 (0.013)	4.02E-09
	N29_N11	0.059 (0.016)	2.45E-04	2.14E-02	0.057 (0.018)	1.71E-03	0.055 (0.013)	9.99E-06
	N31_N12	-0.066 (0.016)	4.06E-05	7.21E-03	-0.079 (0.018)	1.47E-05	-0.074 (0.012)	3.61E-09
	N33_N13	0.06 (0.016)	1.78E-04	1.77E-02	0.05 (0.018)	5.90E-03	0.043 (0.012)	5.67E-04
	N33_N22	0.055 (0.016)	6.52E-04	3.85E-02	0.055 (0.018)	2.76E-03	0.055 (0.013)	1.11E-05
	N39_N33	0.074 (0.016)	4.80E-06	1.43E-03	0.046 (0.018)	1.23E-02	0.047 (0.013)	1.78E-04
	N42_N6	-0.056 (0.016)	4.43E-04	3.13E-02	-0.057 (0.018)	1.80E-03	-0.044 (0.013)	4.75E-04
	N42_N18	0.055 (0.016)	5.77E-04	3.73E-02	**0.035 (0.018)**	**5.63E-02**	0.025 (0.012)	4.60E-02
	N44_N17	0.054 (0.016)	6.21E-04	3.84E-02	0.041 (0.018)	2.33E-02	**<0.001, >-0.001 (0.012)**	**9.68E-01**
	N44_N25	0.071 (0.016)	7.78E-06	1.65E-03	0.057 (0.018)	1.48E-03	0.054 (0.012)	1.19E-05
	N45_N5	-0.058 (0.016)	2.93E-04	2.42E-02	-0.045 (0.018)	1.28E-02	-0.05 (0.012)	7.09E-05
	N45_N15	0.059 (0.016)	2.34E-04	2.14E-02	0.037 (0.018)	4.03E-02	0.039 (0.012)	1.72E-03
	N45_N44	0.055 (0.016)	4.81E-04	3.25E-02	**0.034 (0.018)**	**5.71E-02**	**0.019 (0.012)**	**1.27E-01**
	N46_N25	-0.057 (0.016)	4.00E-04	2.97E-02	-0.039 (0.018)	3.18E-02	**-0.02 (0.012)**	**1.09E-01**
	N47_N31	0.059 (0.016)	1.68E-04	1.77E-02	0.056 (0.018)	1.87E-03	0.034 (0.012)	5.23E-03
	N48_N19	0.061 (0.016)	1.59E-04	1.77E-02	0.046 (0.018)	1.10E-02	0.041 (0.013)	1.14E-03
	N48_N21	-0.061 (0.016)	1.44E-04	1.77E-02	-0.057 (0.018)	1.75E-03	-0.021 (0.012)	8.73E-02
	N50_N7	0.057 (0.016)	3.33E-04	2.60E-02	0.059 (0.018)	1.18E-03	0.057 (0.012)	4.27E-06
Educational attainment	N5_N4	-0.103 (0.031)	1.01E-03	4.54E-02	-0.056 (0.018)	2.28E-03	-0.045 (0.013)	3.91E-04
	N8_N3	-0.119 (0.031)	1.42E-04	1.75E-02	-0.056 (0.018)	2.34E-03	-0.036 (0.013)	4.51E-03
	N12_N5	0.132 (0.031)	2.71E-05	6.71E-03	0.056 (0.018)	2.25E-03	0.033 (0.013)	8.67E-03
	N12_N11	0.106 (0.031)	6.94E-04	3.97E-02	**0.032 (0.018)**	**7.50E-02**	0.038 (0.012)	2.24E-03
	N15_N7	0.122 (0.031)	7.96E-05	1.48E-02	0.041 (0.018)	2.35E-02	0.044 (0.012)	4.66E-04
	N17_N15	0.121 (0.031)	9.59E-05	1.53E-02	0.046 (0.018)	1.21E-02	0.054 (0.012)	1.65E-05
	N19_N18	-0.136 (0.031)	1.47E-05	5.47E-03	-0.058 (0.019)	1.74E-03	-0.039 (0.013)	1.99E-03
	N20_N10	-0.109 (0.031)	4.91E-04	3.80E-02	-0.071 (0.018)	1.28E-04	-0.043 (0.013)	6.06E-04

		Main model			Unrelated people (N~=4k)		Unrelated people (N~=7k)	
	Connection	Beta (std)	$P_{uncorrected}$	$P_{corrected}$	Beta (std)	$P_{uncorrected}$	Beta (std)	$P_{uncorrected}$
	N24_N4	-0.108 (0.031)	6.15E-04	3.80E-02	-0.049 (0.018)	7.95E-03	-0.038 (0.013)	2.33E-03
	N25_N3	0.137 (0.031)	1.36E-05	5.47E-03	0.068 (0.018)	2.36E-04	0.042 (0.013)	8.17E-04
	N25_N4	-0.161 (0.031)	2.73E-07	4.06E-04	-0.081 (0.018)	1.06E-05	-0.077 (0.013)	8.59E-10
	N26_N12	0.108 (0.031)	5.51E-04	3.80E-02	**0.029 (0.018)**	**1.12E-01**	0.032 (0.013)	1.05E-02
	N29_N25	0.108 (0.031)	5.88E-04	3.80E-02	0.042 (0.018)	2.29E-02	0.038 (0.013)	2.75E-03
	N31_N7	0.125 (0.031)	6.57E-05	1.39E-02	0.039 (0.018)	3.21E-02	0.038 (0.012)	2.19E-03
	N33_N2	-0.103 (0.031)	9.96E-04	4.54E-02	-0.064 (0.018)	5.00E-04	**-0.024 (0.013)**	**6.05E-02**
	N34_N26	-0.133 (0.031)	2.14E-05	6.37E-03	-0.051 (0.018)	5.55E-03	-0.059 (0.013)	2.69E-06
	N35_N33	0.108 (0.031)	5.63E-04	3.80E-02	0.055 (0.019)	3.26E-03	0.037 (0.013)	3.41E-03
	N36_N35	0.105 (0.031)	7.79E-04	4.09E-02	0.055 (0.018)	2.59E-03	0.027 (0.013)	3.49E-02
	N40_N7	0.118 (0.031)	1.72E-04	1.96E-02	0.06 (0.018)	1.24E-03	**0.019 (0.013)**	**1.46E-01**
	N40_N34	0.122 (0.031)	1.03E-04	1.53E-02	0.049 (0.018)	7.75E-03	0.044 (0.013)	4.62E-04
	N42_N8	-0.108 (0.031)	5.89E-04	3.80E-02	-0.052 (0.018)	4.56E-03	**-0.018 (0.013)**	**1.55E-01**
	N44_N25	0.112 (0.031)	3.35E-04	2.93E-02	0.047 (0.018)	9.83E-03	**0.012 (0.012)**	**3.30E-01**
	N44_N36	0.139 (0.031)	9.61E-06	5.47E-03	0.071 (0.018)	1.09E-04	0.044 (0.013)	4.38E-04
	N45_N15	0.117 (0.031)	2.05E-04	2.17E-02	**0.028 (0.018)**	**1.33E-01**	0.037 (0.013)	3.59E-03
	N45_N36	0.105 (0.031)	8.20E-04	4.09E-02	0.061 (0.018)	1.07E-03	0.031 (0.013)	1.46E-02
	N45_N44	0.105 (0.031)	6.74E-04	3.97E-02	**0.036 (0.018)**	**5.18E-02**	**0.008 (0.013)**	**5.02E-01**
	N46_N36	0.11 (0.031)	4.54E-04	3.74E-02	0.047 (0.018)	1.09E-02	0.029 (0.013)	1.91E-02
	N47_N36	0.105 (0.031)	7.93E-04	4.09E-02	0.046 (0.018)	1.29E-02	0.028 (0.013)	2.42E-02
	N47_N45	0.11 (0.031)	3.35E-04	2.93E-02	**0.029 (0.018)**	**1.02E-01**	**0.016 (0.012)**	**1.88E-01**
	N48_N5	-0.114 (0.031)	2.75E-04	2.72E-02	-0.061 (0.018)	8.06E-04	-0.046 (0.013)	2.78E-04
	N50_N10	-0.121 (0.031)	1.15E-04	1.55E-02	-0.059 (0.018)	1.31E-03	-0.029 (0.013)	2.30E-02
	N52_N37	0.104 (0.031)	8.37E-04	4.09E-02	0.052 (0.018)	4.74E-03	0.043 (0.013)	5.31E-04
	N55_N10	-0.105 (0.031)	8.53E-04	4.09E-02	-0.074 (0.018)	6.83E-05	-0.027 (0.013)	3.32E-02
Household income	N12_N11	0.072 (0.017)	2.64E-05	9.80E-03	0.063 (0.019)	9.81E-04	0.043 (0.013)	1.17E-03
	N15_N11	0.082 (0.017)	1.60E-06	2.38E-03	0.082 (0.019)	1.91E-05	0.043 (0.013)	1.21E-03
	N18_N8	0.064 (0.017)	2.02E-04	3.34E-02	0.06 (0.02)	2.40E-03	**0.019 (0.013)**	**1.50E-01**
	N18_N12	0.067 (0.017)	9.42E-05	2.01E-02	0.047 (0.02)	1.69E-02	0.035 (0.013)	9.10E-03
	N24_N4	-0.067 (0.017)	9.49E-05	2.01E-02	-0.062 (0.02)	1.65E-03	-0.052 (0.013)	1.23E-04
	N25_N4	-0.062 (0.017)	2.88E-04	3.89E-02	-0.065 (0.02)	9.67E-04	-0.056 (0.013)	2.66E-05
	N26_N12	0.078 (0.017)	6.04E-06	4.49E-03	0.074 (0.019)	1.54E-04	0.062 (0.013)	3.55E-06
	N30_N6	0.062 (0.017)	2.83E-04	3.89E-02	0.049 (0.02)	1.24E-02	0.039 (0.013)	3.19E-03
	N31_N7	0.062 (0.017)	3.19E-04	3.94E-02	0.049 (0.019)	1.09E-02	0.035 (0.013)	7.45E-03
	N34_N26	-0.073 (0.017)	2.01E-05	9.80E-03	-0.079 (0.02)	5.35E-05	-0.071 (0.013)	1.25E-07
	N40_N2	0.06 (0.017)	4.27E-04	4.23E-02	0.041 (0.019)	3.63E-02	**0.024 (0.013)**	**7.07E-02**
	N40_N19	0.06 (0.017)	4.06E-04	4.23E-02	0.051 (0.019)	8.10E-03	0.044 (0.013)	8.49E-04
	N40_N22	-0.061 (0.017)	3.84E-04	4.23E-02	-0.073 (0.02)	2.14E-04	-0.051 (0.013)	1.51E-04
	N44_N40	0.065 (0.017)	1.40E-04	2.59E-02	0.062 (0.019)	1.58E-03	0.042 (0.013)	1.58E-03
	N47_N18	0.068 (0.017)	7.42E-05	2.01E-02	0.053 (0.02)	6.36E-03	**0.024 (0.013)**	**7.24E-02**